VOLUME 1 • SEPTEMBER 1959 • NUMBER 3

A.M.A. ARCHIVES OF NEUROLOGY

Dynamics of Neuromuscular Diseases
A. A. Marinacci

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Thomas W. Langfitt and Louis A. Finney

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Cerebellar Pathology in an Infant Resembling Chick Nutritional Encephalomalacia
M. K. Horwitt and Percival Bailey

A Study of Coagulation Factors in Blood and Spinal Fluid in Multiple Sclerosis
Spencer D. Albright III, Henry G. Kupfer, and Dixie R. Kinne

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References: **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.

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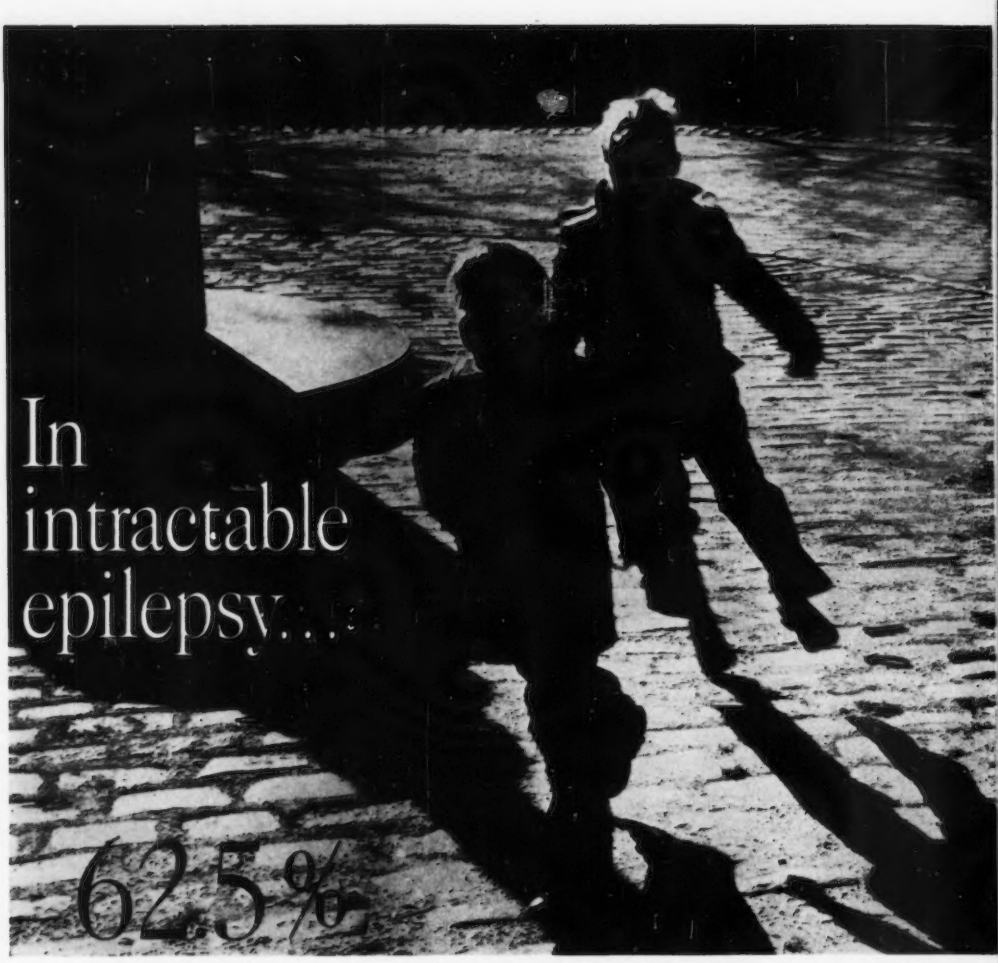

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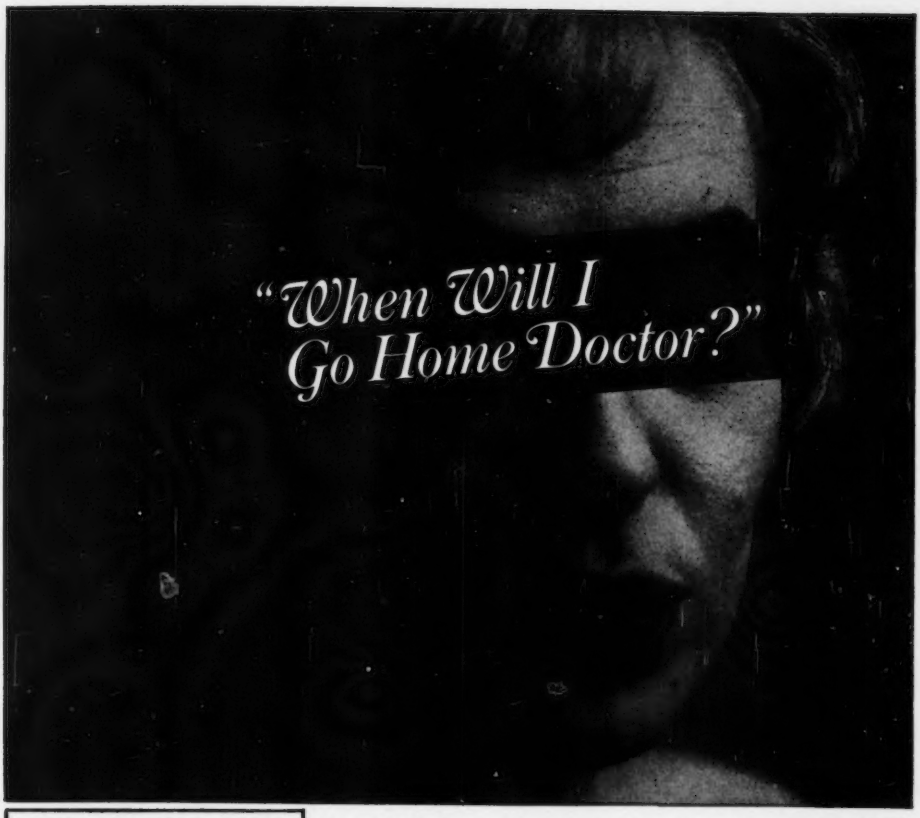

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destructive and assaultive,
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atient in light sleep.
an be awakened readily,
nd responds to questioning.

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NEUROLOGY

Dynamics of Neuromuscular Diseases

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For the past 30 odd years, electromyography has been used to aid in the understanding and investigation of abnormal function or of dysfunction of the lower motor neuron, more specifically of the motor unit. During the latter part of this period, clinical electromyography has been developed specifically to understand the abnormality of dysfunction of the lower motor neuron (neuropathies) as well as of the muscle itself (myopathies). As a result of these clinical studies, some questions have arisen regarding the true nature of denervation activity. For example, is this activity an inherent property of the skeletal muscle fiber as an organ itself, having existed from intrauterine life? Is denervation activity a reversion of the inherent function of the muscle fibers to their infantile preinnervated state? It is assumed that the motor nerve has two basic controls over the muscle fibers: (*a*) trophic control, and (*b*) physiological control of its excitable sarcolemma contractile mechanism. When a peripheral motor nerve is interrupted, loss of these controls is manifested by (1) trophic structural changes (muscular atrophy) and (2) cessation of normal neuromuscular activity (paralysis). In the place of the neuromuscular normal voluntary contractile factor, there appear two functional changes. One of these is an independent spontaneous contraction (twitching) of the muscle fiber, the purpose of which seems to be to ensure its own survival. This spontaneous activity is referred to as fibrillation of denervation. The second change is that the excitable sarcolemma mechanism, freed from its motor nerve, is now at the mercy of any other intercurrent chemical or mechanical stimulant. The resultant activity is known as positive sharp waves.

There arises the question what relation this altered physiological state has with the original embryonic development of the normal neuromuscular contractile mechanism. It may also be queried whether the electromyogram would be of any value in a study of these altered effects from a viewpoint of its embryological physiology. In order to answer the above question, it would be necessary to obtain pertinent information from living human fetuses with the aid of this modality. By such means, it would be possible to follow the embryonic development of the musculature and its ultimate innervation. As a practical means of accomplishing this purpose, a series of electromyograms were made of the muscles of premature living human infants. In order to complete the picture, a series of electromyographic studies of abnormal neuromuscular states of early life were undertaken to explore characteristic electromyographic activity generated by these normal and abnormal states.

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Of these various questions, special attention is to be given to the matter of reversion to infantile preinnervation activity after the muscle fiber is separated from the motor nerve. Other examples of this reversion to infantile activity is seen in many phases of dysfunction. Under these circumstances, the electroencephalogram reverts from alpha (adult) activity to delta (infantile) activity, as does the electrocardiogram from normal adult to fast infantile rhythm. This is comparable to a physiological alteration of functions in the development of the Babinski sign. Such a sign is present in the infant from birth until he begins to walk and reappears whenever an upper motor neuron lesion occurs. The same can be said of the grasp reflex and certain aspects of coordination.

I believe that this reversion phenomenon might best be studied by using the electromyogram in the following seven conditions: 1. The muscles of premature living human infants were studied, the length of whose gestation period would be comparable to the actual development of the neuromuscular mechanism. 2. Such infantile activity could be further observed in the muscles of the lower extremities which have not become innervated owing to an interference with their growth by a gross lesion, spina bifida (myelomeningiocystocele). 3. In another approach to the problem, infants were studied who presented signs of disease of the lower motor neuron, such as infantile (spinal) muscular atrophy (Werdnig-Hoffmann disease). 4. An investigation was also made of the electromyographic changes in examples of infantile polyneuropathy, mononeuropathy, and (5) myopathies occurring in early life. 6. For comparison, an examination of the muscles of apparently normal infants was done. 7. In the last group, attention is called to a small number of adults in whom certain aberrant electrical dysfunctions which resemble infantile activity are sometimes found during routine electromyography. Before investigating these phenomena, however, it is necessary to review the simultaneous development of the skeletal muscles and the peripheral nerves.

Embryology of the Skeletal Muscles

A very useful description of the development of skeletal muscle fibers in the human embryo from the 10th week of intrauterine life to full term has been made by Cuajunco in 1940-1942.[1,4] This investigator has noted that an individual skeletal muscle can be identified as early as the 7th week of intrauterine life, and that by the 10th week small, but well-formed, muscle fibers can be clearly identified. The histological structure of these original fibers is embryonic in appearance, as shown by the central position of their nuclei. The true sarcolemma is not yet visible at the 10th week, and thin myofibrils can be seen only beneath the outer limits of the cell. The transverse striations at this period are faintly identified only in the muscles of the neck, trunk, and shoulders, not in the muscles of the arms and legs. In the 11th week, the diameter of the muscle fibers has increased, and the myofibrils are more abundant, filling the cells more completely. The transverse striations are now more in evidence in the muscles of the proximal portion of the arms. By the 11th week, the distal muscles are as well developed as were the shoulder muscles at 10 weeks. By the 12th week, the muscle fibers have become thicker, the myofibrils are more abundant, and the striations are more prominent. Longitudinal splitting of the individual muscle fibers is seen for the first time. During the 13th week, the myofibrils are still more evident, and the nuclei of the muscle fibers have begun to move from their central location to the more peripheral aspects of the fiber. The myofibrils are now compressed into columns. Splitting of the fibers continues during the 13th and 14th weeks, when the myofibrils become grouped into definite bundles. The striations are now prominent, and splitting of the muscle fibers is very active. By the 15th week, one can visualize two distinct sizes of muscle fibers, large

and small. The larger fibers have only very little clear sarcoplasm in the center. The striated myofibrils are prominent, and the nuclei are now peripherally located. These early-developed muscle fibers are referred to as "mother" fibers and appear to be the first elements to be innervated (between the 12th and the 15th week). These parent fibers continue to divide, giving rise to smaller fibers, referred to as "daughter" fibers. Splitting of these fibers apparently ceases about the fifth month of intrauterine life. It has been assumed by some that the enlargement of the muscle fibers during the second half of intrauterine life is due to an increase in their number. New muscle fibers evidently continue to form throughout entire fetal life, and even after birth, for Tello in 1917 [2] states that the new fibers can be seen in the full-term human fetus. It would seem, therefore, that the preinnervation fibrillation recorded by the electromyogram in early infancy is derived from these daughter fibers, which are not yet innervated. The mother fibers are apparently innervated simultaneously as they develop. On the other hand, the daughter fibers are not innervated while they are being separated from the mother fibers. Their innervation seems to be a rather gradual process, as shown by the electromyographic findings in premature infants.

Development of the Neuromuscular Mechanism

The embryogenesis of the motor end-plate and sensory organs of the skeletal musculature has been studied in great detail by Tello in 1917 and 1922,[2,3] and more recently by Cuajunco in 1940 and 1942.[1,4] Nerve fibers can be observed in the connective tissue during the 10th week of intrauterine life. Terminal twigs of the peripheral nerves apparently come into contact with the muscle fibers by the 11th week. Progressive growth of the nerve fibers is closely followed by migration of connective tissue cells which are to become the cells of the sheath of Schwann and the specialized endoneural sheath of Henle. The terminal fibrils of the nerve branch to form the telodendria, which are in close contact with the surface of the muscle fibers. By the 13th week, the protoplasm of this group of cells fuses with the group of sarcolemma nuclei to form an elevation known as Doyère's eminence. From the 14th to the 24th week of fetal life the motor nerve endings undergo complete reorganization.

Tello, in 1917 and 1922,[2,3] and Cuajunco, in 1940 and 1942,[1,4] have also reported on the embryogenesis of the neuromuscular spindle. The earliest state of formation of this structure is about the 11th week of fetal life, at which time it can be recognized only as spiral nerve endings around the myoblasts. The capsule begins to form by the 12th week, and it rapidly surrounds the bundle of muscle fibers, which receives the nerve endings to form a spindle-shaped sheath. This bundle is formed fully about the 14th week. By this time the larger nerve fibers are beginning to be myelinated, and by the 24th week many of the nerves are well myelinated. During this period the motor fibers form a motor end-plate on each muscle fiber of the spindle. During the process of myelination and formation of the motor end-plate, the cells of Schwann fuse with the sarcolemmal nuclei of the muscle fibers. At the same time, progression of innervation to form the motor end-plate and fusion of the cells of Schwann with the sarcolemmal nuclei go on in the remainder of the muscle fibers. By this fusion the muscle then becomes wholly dependent upon the motor nerve for its trophic effect, and the nerve also suppresses the spontaneous independent excitation contractile mechanism of the sarcolemma. Whenever the muscle fibers are again separated from this control (as a result of nerve degeneration) the muscle fibers revert to their embryonic preinnervated state of independent spontaneous twitching (fibrillation). Also, the suppression control on the excitation of the sarcolemma being no longer present, the muscle fibers contract independently, creating the positive sharp wave. In cases where

the trophic control is intact but the excitable sarcolemmal mechanism is not under the control of the nerve, there will be no fibrillation of denervation, but positive sharp waves will be seen during mechanical stimulation, as seen in myotonia. At the time of innervation, the muscle fibers are very small but have all their typical morphological characteristics. Following innervation, therefore, the muscle fibers increase only in size, that is, in thickness and in length.

Bardeen, in 1900,[5] has pointed out that the muscle fibers of the embryo are differentiated to a considerable degree before the nerve connections are established.

In exogastrulae where the muscle fibers develop but are not innervated they soon disappear. Up to the present time, the fate of muscle fibers in mammals where innervation does not occur was unknown. With the aid of the electromyogram, however, the fate of these noninnervated muscles is clarified. This is demonstrated by a study of the activity generated from such muscles in premature infants and in other conditions where innervation has failed to take place. In addition, in teratomas striated muscle fibers have survived for long periods of time without apparent innervation.

It is of specific clinical, as well as of physiological, interest to know that the neuromuscular system has a specific course of development and of movement. This development follows an orderly fashion and can be quite accurately predicted. The muscles of the neck and trunk are the first to develop; then come the muscles of the tongue and face, following which the muscles of the shoulder girdle appear, and only then are formed the muscles of the proximal and, finally, the distal parts of the extremities.

Muscles of the upper extremities appear to be mature before those of the lower extremities. The muscles of the feet are the last to mature. Therefore, the development progresses in the axial groups from the neck to the pelvis, and in the appendicular ones from the proximal to the distal parts of the extremities.

In passing, it is well to point out that the appearance of denervation activity follows precisely the embryonic development of the neuromuscular system itself. For example, in diseases of the anterior horn cells, such as anterior poliomyelitis, or nerve root lesions, such as neuronitis or nerve-root-compression syndrome, denervation activity is detected about the 12th day in the paraspinal muscles of the trunk, while it takes about 18 to 21 days before denervation activity appears in the extremities.

It is well known that the fetus first retracts the head with the muscles of the neck, then uses the muscles of the trunk, followed by those of the shoulder girdle, before moving the hands and fingers; and, finally, movements of the feet occur. Thus, fetal movement from cephalad to caudad and from the upper to the lower extremities follows an orderly pattern of development of the muscles and the motor innervation of the muscles during fetal life. This progression of development of the neuromuscular system and the time of innervation of such muscles is further substantiated by fetal movements, which can be first perceived by the pregnant woman during the fourth month of pregnancy. This is the time at which the organization of the neuromuscular system begins to mature in the neck and trunk musculature.

Basic Differences Between Adult Denervation and Preinnervation Infantile Activity

Adult denervation potentials are from 10μv. to 200μv. in amplitude and from 1 to 2 msec. in duration, and have a frequency up to 30 per second, the waves being both monophasic and diphasic, with a high-pitched, clicking sound. The potentials are easily discerned on both the loud speaker and the oscilloscope. In partial lesions there are usually both polyphasic and nascent motor units, denoting demyelination and/or nerve regeneration. The positive sharp waves produced by mechanical stimulation are large and have a high frequency. The motor units are from 2 to 30 msec. in dura-

tion, with amplitudes up to 4 mv. Giant motor units are also present, as described by Marinacci in 1955.[6] This type of activity may be readily studied with the aid of either the monopolar or the coaxial needle electrode.

Preinnervation infantile activity is very small, mostly in the form of monophasic waves; the duration varies from 0.5 to 1 msec.; the frequency is not more than 10 per second, and the amplitude is usually not above 15μv. This activity can readily be discerned on the loud speaker but is difficult to see on the oscilloscope. On insertion of the electrode, positive sharp waves are activated, being very small, up to 30μv., and about 3 msec. in duration. No giant, polyphasic or nascent motor units are present, suggesting that neurotization and myelination take place more or less simultaneously. Normal motor units are very small, and are mostly monophasic or diphasic, triphasic waves being rarely recorded. The duration is 1 to 3 msec. and up to about 100μv. The frequency ranges up to 40 per second during strong contraction, thereby resembling dystrophic activity, as described by Marinacci in 1954.[7] The individual motor units can be recorded distinctly with either the monopolar needle or the coaxial needle electrode. Preinnervation infantile activity can be distinctly recognized when explored with the monopolar needle electrode, whereas with the coaxial electrode it is difficult to elicit them.

In short, the essential differences between preinnervation infantile activity and the adult type of denervation are that adult denervation activity is higher in voltage, as well as in frequency. In the infantile activity, on the other hand, no demyelination is seen; the potentials are very small, being heard from the loud speaker but not seen on the oscilloscope, and are difficult to record with the coaxial needle. Nevertheless, these potentials can be detected with the monopolar technique.

It is now necessary to show how the characteristics of preinnervation activity were discovered. This was accomplished by (1) a study of preinnervated muscles in premature infants, (2) an evaluation of muscle potentials in the lower limbs in case of severe degrees of spinal bifida, (3) noting the nature of the potentials in infantile muscular atrophy, and (4) a study of the (*a*) neuropathies, and (*b*) myopathies in infancy, (*c*) residual preinnervation infantile activity in normal infants, and (*d*) subclinical myopathies in later life.

Electromyogram in Premature Infants

An electromyographic study was done on 11 premature infants in an effort to determine the nature of muscle reaction during this period. The areas most frequently examined were the paraspinal muscles of the neck and the middorsal and lower lumbar region, the deltoid in the arm, the extensors in the forearm, the gastrocnemius in the leg, and the interossei in the foot.

The paraspinal muscles of the neck in all the cases showed normal insertion activity. Under voluntary efforts, the motor units were very small in duration and in voltage. The duration was about 1 to 3 msec. and the voltage from 10μv. to 100μv. The frequency varied according to the contraction, from about 5 to 40 per second. About 5% to 10% preinnervation infantile activity was recorded most frequently in the paraspinal muscles of the lower lumbar region, while in the gastrocnemius and in the muscles of the feet it varied up to from 10% to 20% in the areas sampled. Insertion of the needle produced prolonged mechanical activity in the form of positive sharp waves. The spontaneous preinnervation infantile activity which was recorded was very small in amplitude, up to 15μv., and very short in duration, 0.5 to 1 msec.; and the frequency ranged up to 10 per second.

The most characteristic phenomenon which was encountered as far as this preinnervation infantile activity was concerned was that it was acutely perceptible over the loud speaker, whereas the gain had to be increased considerably before the potentials were discernible on the oscilloscope. Ap-

parently, this illustrates the basic phenomenon of the instantaneous detection of the sound by the ear, while some latent period exists in the visual chemical reaction of the human retina. It is apparent that the small motor units generated during voluntary efforts; the positive sharp waves and fibrillation potentials are consistent with the very small size of the muscular fibers in the premature infant. One is impressed with the fact that without the aid of the loud speaker one would be unable to discern this very small preinnervation infantile activity.

It was noted that the motor units in the muscles of the neck were somewhat larger than those in the lower extremities. This is apparently due to the fact that the musculature of the neck is developed much earlier than the muscles of the extremities. It was further noted that the amount of preinnervation activity was more or less in proportion to two things: (1) The shorter the period of gestation, the more infantile preinnervation activity was evident, and (2) the smaller the infant, the more infantile preinnervation activity was present. One was also impressed with the lack of polyphasic motor units. In fact, no units of this type were recorded in this study, the activity being mostly simple and diphasic, triphasic units not being seen. This suggests that the processes of neurotization and myelination are essentially simultaneous.

On insertion of the needle electrode, high-frequency positive sharp waves were rather frequent in the muscles in which fibrillation was recorded. But these were also very small. There were no excursions and no waning phase, such as is seen in myotonia. This indicates that the preinnervated muscle fibers in fetal life are hyperirritable, just as they are in denervated muscles in later life. This is to say, the preinnervated infantile skeletal muscle fibers are also at the mercy of any type of stimulation. It was noted that in muscles in which no preinnervation activity was found there was no hyperirritability of the muscle fibers. This again suggests the fact that when the motor end-plate fuses with the sarcolemma, the nerve fibers have full control over the excitable mechanism of the muscle fibers. Such control is lacking in myotonia. It is further noted that there were no nascent motor units recorded in the premature infant, as seen in reinnervation in adult life. This again suggests that myelination and neurotization take place more or less simultaneously.

The low voltage of the motor units in fetal life appears to be the result of the fact that the muscle fibers have not yet fully developed. From the above findings, one can draw the following conclusions as to the significance of preinnervation infantile activity: Muscle fibers twitch or fibrillate before innervation takes place in intrauterine life; fibrillation is, therefore, an inherent property of the independent muscle fibers and a necessity for survival. In addition, the preinnervated muscle fibers are hyperirritable. Innervation is a gradual process, proceeding from cephalad to caudad in the axial (truncal) muscles, then to the upper and, finally, to the lower extremities. The myelin sheath and the axons mature simultaneously, and fusion of the motor end-plate with the sarcolemma occurs about the same time. For this reason, there are no polyphasic motor units, indicating that demyelination has not occurred.

All of the above recordings were made with the unipolar needle, in which there is a considerable distance between the active and the reference electrode. Recording with the coaxial needle was attempted. However, only motor units were recorded during voluntary efforts, and these were smaller than those recorded with the unipolar needle. Preinnervation activity could hardly be perceived with the coaxial electrode. In fact, most of this activity was canceled out with the coaxial needle. Because the distance between the reference and the active electrode in the coaxial needle is negligible, the very tiny denervation potentials generated by embryonic muscle fibers were more or less canceled out.

Cases of only 4 of the 11 premature infants will be presented, as some of these cases had similar findings.

CASE 1.—A 4-day-old girl was born on Oct. 25, 1958, weighing 2 lb. 11 oz. (1,219 gm.) at birth. Gestation was estimated to be six months. This infant was one of twins. The other twin was not examined but weighed 2 lb. 7 oz. (1,106 gm.). The electromyogram on Oct. 29 revealed small motor units from the muscles of the neck during voluntary contraction. The motor units had a duration of 1 to 3 msec. and amplitudes up to 200μv. The frequency ranged from 5 to 30 per second. No polyphasic motor units were noted. In the paraspinal muscles in the low lumbar region, normal motor units were generated during voluntary contraction, but no polyphasic motor units were recorded. Tiny fibrillations, up to 15μv. and with a duration between 0.5 and 1 msec. were recorded. Needle insertion activated small positive sharp waves up to 3 msec. in duration, the discharges lasting about three seconds. This activity was acutely detected from the loud speaker but hardly discernible on the oscilloscope. Preinnervation infantile activity was found in about 5% to 10% of the areas sampled in the lumbar region and in 10% to 20% of the areas sampled in the left gastrocnemius. All the motor units were simple; no polyphasic activity was recorded.

Comment.—These findings indicate that a certain number of muscle fibers in the lumbar region, and more in the lower extremities, were not innervated and that their behavior was similar to that of adult denervation. The only exception was that no polyphasic motor units were present.

Another interesting point is that the above recordings were done with both the monopolar and the coaxial needle electrode. The monopolar electrode gave the above findings, while with the coaxial needle electrode denervation potentials could be perceived only faintly from the loud speaker. It is apparent that when one deals with very tiny potentials the coaxial needle appears to be of no value. In fact, the small potentials recorded during voluntary contraction, as well as during relaxation (fibrillation), result from the fact that the muscle fibers are very tiny at this stage.

The next case presents somewhat variable degree of denervation activity. This seems to be related to the weight of the infant.

CASE 2.—A 6-day-old girl, who was born on Nov. 3, 1958, weighed 4 lb. 7 oz. (2,013 gm.). The estimated gestation period was 6½ months. The electromyogram taken on Nov. 9 included the following muscles: paraspinal muscles of the neck and lower lumbar area, the right deltoid, and the right extensors in the forearm. All the activity recorded in these muscles was that of normal infantile motor units, with no denervation activity. About 5% preinnervation infantile activity was recorded in the distal half of the gastrocnemius and in the muscles of the feet. Only minimal fibrillation was recorded in the paraspinal muscles of the lumbar region.

Comment.—Here, again, the motor units and preinnervation infantile activity were small, and no polyphasic motor units were found. The preinnervation activity which was present was certainly less in degree, and the neuromuscular maturity was consistent with progression from cephalad to caudad and then to the extremities. Here, again, with the coaxial needle electrode, preinnervation infantile activity could hardly be detected. Thus, the muscle fibers which are not yet innervated follow the course of development.

In the following case, it was fortunate to have the opportunity of obtaining two electromyograms on the same infant, one when the infant was 7 days old, and the second when the child was 3 months old.

CASE 3.—A 7-day-old girl was born on July 29, 1958, and weighed 2 lb. 2 oz. (964 gm.). The gestation period was about six months. The electromyogram on Aug. 5 showed normal motor unit activity in the muscles sampled. In addition, about 5% to 10% spontaneous preinnervation activity was heard in the left deltoid and lower lumbar muscles and about 15% to 20% in the gastrocnemius.

The electromyogram on Nov. 7, when the infant weighed 5 lb. 2 oz. (2,325 gm.), showed no fibrillation in the muscles of the neck or shoulder girdle, with one or two fibrillations in the right forearm and about 5% in the gastrocnemius and first dorsal interossei.

Comment.—The comparison of the electromyograms suggests that a considerable amount of development of the neuromuscular spindle had taken place in the three months between the two electromyograms and that the muscle fibers in the extremities were being innervated gradually. Again, no

signs of demyelination (polyphasic motor units) were found, and the preinnervation infantile activity which was present was no different from that found in the rest of the cases, described above. Some positive sharp waves were seen with fibrillation.

The last case of the premature infants presents another variation in maturation of the neuromuscular spindle in that no changes were found except in the muscles of the feet.

CASE 4.—An 11-week-old boy was born on Aug. 10, 1958, and at birth weighed 4 lb. 3 oz. (1,899 gm.). The electromyogram taken Oct. 30, when the infant weighed 5 lb. 4 oz. (2,381 gm.), showed normal activity in the muscles of the neck, the left deltoid, the extensor group in the left forearm, the low lumbar paraspinal muscles, and the gastrocnemius. Minimal preinnervation infantile activity was found in the first dorsal interossei of the left foot.

Comment.—This case suggests that maturation of the neuromuscular spindle varies from one patient to another.

Other observations made in this series of 11 cases indicate that the findings in twins seem to be identical, although they are not necessarily so in two infants of apparently the same gestation period. This would suggest that some individual variation in the development of the neuromuscular spindle does occur. There also seems to be some relationship between the body size of the fetus and the maturity of the neuromuscular spindle.

From the above findings it appears that about 5% to 15% of the muscle fibers continue to be innervated in the last three and a half months of intrauterine life. By the last month of intrauterine life only about 5% are still in the process of innervation.

According to these observations, preinnervation activity has its own characteristics: 1. The potentials are extremely small, both the spontaneous and the mechanical. 2. There is no evidence of demyelination, as indicated by the fact that polyphasic motor units are absent. 3. Finally, innervation follows a specific pattern in the trunk from cephalad to caudad, and in the extremities from proximal to distal.

Electromyogram in Cases of Spina Bifida

I have had occasion to examine a considerable number of younger patients with spina bifida, which is a general term applied to a group of congenital abnormalities of the meninges and spinal cord. These lesions usually occur in the lumbar and sacral regions. In this connection, the cases studied were of the incomplete form of spina bifida, of which there are several varieties. In those cases in which one deals with only spinal meningocele, that is, in which the hernial sac contains only clear fluid, the electromyogram is normal. On the other hand, in those cases in which the sac contains the spinal cord and associated nerve roots (meningomyelocele), the electromyogram is found to be abnormal. The electromyographic findings recorded from these cases are of two degrees, complete and incomplete. These cases are of interest in this connection because the preinnervation activity found in the muscles not yet innervated because of the congenital defect further substantiates the fact that skeletal muscle fibrillates before it is innervated in intrauterine life.

Only two cases have been examined specifically with this phenomenon in mind. The first case demonstrates that a certain number of axons did get through to innervate certain portions of the muscles of the lower extremities.

CASE 5.—A 13-day-old girl who was born on Oct. 14, 1958, weighed 3 lb. 2 oz. (1,417 gm.) at birth. The approximate gestation period was 6½ months. Clinically the patient presented a large meningomyelocele over the lumbar spine. The electromyogram of Oct. 27 included examination of the paraspinal muscles of the neck and middorsal region, which were normal, as was the right deltoid. In the midlumbar region, only about 5% preinnervation activity was found, just above the meningomyelocele. In the gluteal group, with the quadriceps and gastrocnemius under a state of contraction, infantile motor units were recorded which were about 2 to 3 msec. in duration and up to 100μv. No polyphasic motor units were seen. However, about 60% preinnervation activity and small positive sharp waves were recorded in the gluteal group, quadriceps, and gastrocnemius bilaterally. The preinnervation activity was more abundant distally.

Comment.—In this case only about 40% of the axons had innervated (from L 4 distally) the muscles of the pelvic girdle and lower extremities, while 60% of the axons did not reach the muscles of the lower extremities because of the interposed congenital defect. Here, again, we found no polyphasic motor units, denoting that spontaneous activity was preinnervation in type. This conclusion was further substantiated by the absence of polyphasic motor units.

The next case is that of a complete meningomyelocele in a patient who underwent surgery. The findings substantiated the assumption that fibrillation is an inherent property of skeletal muscle fibers.

CASE 6.—This patient was a 14-month-old girl, born on Aug. 1, 1957. At birth she weighed 5 lb. 9 oz. (2,523 gm.). The gestation period was 6½ months, the last menstrual period being on Jan. 27, 1957. Roentgenograms taken one week prior to surgery showed absence of the upper sacral neural arch and the presence of a large protrusion. Surgery performed on Aug. 14, 1958, by Dr. Peter Rocovich, disclosed that a large bundle of nerve roots ended blindly in the sac. The patient was able to flex the thighs on the abdomen, but there was complete paralysis below the knees. An electromyogram on Nov. 6, 1958, revealed that the muscles of the neck and upper extremities and the paraspinal muscles of the thoracic region were normal. Normal motor units were also recorded in the quadriceps, but there were no polyphasic motor units and preinnervation activity was present. No motor units were recorded in the gluteal group, hamstring muscles, or the muscles of the legs or feet. However, preinnervation activity was recorded in the gluteal group, hamstring muscles, and muscles of the legs and feet. Insertion of the needle resulted in very small positive sharp waves, up to 30μv., and the fibrillation was small, from 0.5 to 1 msec. in duration. This activity was scarce in some areas and more abundant in others. Nevertheless, the amplitude never ranged above 30μv. Only in the quadriceps did the fibrillation go up to 100μv. This observation indicated that some of the preinnervated muscle fibers continue to hypertrophy in company with normal activity. Infantile activity in the quadriceps was more marked and more abundant. It resembled more closely the activity recorded from adult denervated muscles. However, in the muscles of the legs and feet, activity was infantile in type.

Comment.—The electromyogram revealed in this case that down to nerve roots L 1 and L 2 innervation had followed a normal course, while activity from L 3, L 4, L 5, and all the sacral nerve roots was absent. This case further demonstrates two specific points: 1. Muscle fibers, not innervated themselves but coexistent with innervated ones, continue to mature to a certain extent. In the meantime, they continue to exhibit their inherent contractile activity. 2. The second group of muscles which had not been innervated all showed preinnervation fibrillation. Apparently there was a lack in this case of neighborhood normal activity, so that some degree of functional maturation could continue. The absence of polyphasic motor units denoted lack of nerve regeneration and no demyelination.

Electromyogram in Infantile Muscular Atrophy

Infantile muscular (spinal) atrophy usually is apparent at birth or becomes evident during the first few weeks of life. The presenting clinical picture in these infants is usually one of muscular weakness, hypotonia, and loss of reflexes. The essential pathological change seems to be a result of failure of development and/or subsequent degeneration of the anterior horn cells of the spinal cord and the motor nuclei of the brain stem. The electromyogram has been found to be very useful in the differential diagnosis in this type of disease entity. In the first few months of infancy, it is difficult to distinguish clinically whether the muscular weakness or hypotonia is due to lower motor neuron disease, a peripheral neuropathy, a myopathy, or other possible factors. In mononeuropathy, of course, the changes will be found in the periphery, as will be subsequently explained. However, in typical Werdnig-Hoffmann disease the findings are typical, as demonstrated by the following case.

CASE 7.—This male infant, aged 3 months, was born July 12, 1958, and weighed 8 lb. 2 oz. (3,685 gm.) at birth. He was apparently a full-term infant. From the time of birth he was unable to move either the upper or the lower extremities, and it was thought that he also had some difficulty in breathing. This condition persisted and

became somewhat worse, so that at the time of the electromyographic examination, on Oct. 7, the patient was having respiratory difficulties, for which oxygen was administered. Electromyography was done on the orbicularis oris, supplied by the 7th cranial nerve; the trapezius, supplied by the 11th cranial nerve; the C 1, C 2, and C 3 nerve roots; the right and left extensor groups; the paraspinal muscles at the midcervical, midthoracic, and lower lumbar regions; the quadriceps, and the gastrocnemius bilaterally. Only a few motor units were recorded during reflex action, but no polyphasic motor units and no fasciculations were elicited. However, preinnervation activity was found, consisting of positive sharp waves and active fibrillation recorded from all the muscles sampled. However, the voltage was small, up to 25μv., only one or two having amplitudes up to 100μv. The duration was from 0.5 to 1 msec., with the frequency varying from 2 to 5 per second, with some waves up to 10 per second in some areas. The lack of polyphasic motor units (demyelination) and the infantile type of preinnervation activity strongly suggested that the lower motor neuron had never fully developed in this patient.

Comment.—This case demonstrates what appears to be a typical failure of development of the motor nuclei of the brain stem and the lower motor neuron in the anterior horn cell of the spinal cord in an example of Werdnig-Hoffmann disease. This again proves the point that the muscle fibers twitch before they are innervated and that infantile muscle fibers are hyperirritable during mechanical stimulation.

Many infants have been examined in whom the progressive degeneration of the anterior horn cell was present in the first year of life. In these cases one usually finds fasciculation; and, in addition to the denervation activity, signs of demyelination (polyphasic motor units) are present. Apparently, we have two types of cases—one in which the cells fail to develop, as demonstrated in the above case, and the other in which there are fasciculations and signs of demyelination occurring after birth.

Electromyographic Findings in Polyneuropathy and Mononeuropathy in Infants

Infants have been observed shortly after birth who manifest signs of peripheral neuropathies, such as peroneal-nerve involvement, stretching of the brachial plexus (Duchenne-Erb paralysis), and even acquired peripheral neuropathy, as described by Marinacci and Courville in 1958.[8] With the electromyogram one can determine whether such paralysis occurred during intrauterine life, at birth, or shortly thereafter, as illustrated by the next three cases.

Case 8.—A 6-week-old girl, who was entirely normal with the exception of a left foot drop, which had been present since birth, was brought to the physician for evaluation. It was difficult to differentiate clinically whether the patient had a peripheral nerve or a cerebral lesion. An electromyogram taken on July 14, 1955, showed that the paraspinal muscles were normal, as well as the rest of the muscles of the right lower extremity. However, one or two fibrillations were found, without polyphasic motor units, in the first dorsal interossei of both feet. In addition, infantile fibrillation was found in all the muscles of the left leg supplied by the peroneal nerve. No motor unit activity, either simple or complex, was recorded. Finally, after subsequent electromyograms showed no regeneration of the left peroneal nerve, surgical exploration was carried out, on Oct. 4, 1956, by Dr. Henry M. Cuneo. It was discovered that the course of the nerve was continuous but was very thin and tenuous below the head of the fibula. Electrical stimulation of the left peroneal nerve produced no response, while a normal response was elicited on stimulation of the left tibial nerve.

Comment.—The electromyographic findings in the distribution of the left peroneal nerve indicated that some type of pressure in intrauterine life pervented the axons of this nerve from following their normal course. This further demonstrated that focal peripheral nerve lesions can be specifically localized by the electromyogram in the first few weeks of life. The few fibrillations which were recorded in the interossei of both feet without demyelination indicated that a few of the muscle fibers are still in the process of innervation after birth, or that these fibers had not been innervated at all.

Stretching of the upper trunk of the brachial plexus sometimes occurs as a complication of delivery. Nevertheless, the electromyogram is able to demonstrate whether such injury had taken place or

whether the paralysis was due to some prenatal disorder.

CASE 9.—This 3-week-old girl presented paralysis of the right upper extremity, with apparent impairment of abduction of the shoulder girdle. The electromyogram revealed denervation activity, together with positive sharp waves. The denervation activity varied in amplitude from 20μv. to 50μv. Positive sharp waves were small also, but were heard and identified on the oscilloscope. Under reflex action a few motor units were generated which were polyphasic in nature. This abnormality was found in the following muscles: the supraspinatus, deltoid, biceps, and brachioradialis. The rest of the muscles were normal.

Comment.—The electromyographic findings in this case indicated that the lesion was in the upper trunk of the right brachial plexus, a typical Duchenne-Erb paralysis, and that it was an acquired lesion. This was proved by evidence of demyelination, which is not found in the infantile or preinnervation type of activity. The fibrillations were also much higher in voltage than is found in infantile fibrillation. This child was rechecked six months later and showed more evidence of regeneration (polyphasic motor units), and one year later almost total recovery had taken place.

Polyneuropathy in infants is rather common, although diagnosis is difficult. Such cases present a problem in differential diagnosis between Werdnig-Hoffmann disease, muscular dystrophy, and cerebral palsy.

CASE 10.—This patient was a girl, aged 4 months, and was observed to have weakness and hypotonia in both lower extremities. The usual diagnoses which go with such a distribution of muscular weakness were entertained. The deep reflexes were absent. The electromyogram revealed normal activity in the paraspinal muscles, as well as in the upper extremities. In the lower extremities, however, there was denervation activity, which was nearly adult in type, and a few polyphasic motor units. These findings were present in moderate degree in the gluteal group and thighs, with a considerable amount in the muscles of the feet and legs. The distribution of the denervation activity was typical of polyneuritis in infants.

Comment.—In this case, denervation activity was restricted to the lower extremities, being more pronounced peripherally. Fibrillation was larger than that usually found in the preinnervation type. In addition, polyphasic motor units denoted that demyelination was likewise present, placing this patient in the group of acquired polyneuropathies.

Myopathies in Early Life

Infantile muscular dystrophy is sometimes identified as amyotonia congenita (Oppenheim's disease), as described by Adams et al. in 1953.[9] Intrauterine fetal movements are usually described by the mother as "very weak." At birth in typical cases the infant lies motionless and flaccid (hypotonia). He does not respond to painful stimuli. However, this weakness does not affect the bulbar musculature, and therefore the child does not have the respiratory difficulties such as may be seen in Werdnig-Hoffmann disease. All of the deep reflexes are absent, and electrical response of the muscle is reduced but not completely lost, as is seen in Werdnig-Hoffmann disease. The pathology of the disease has been under some dispute. However, most investigators have found predominant changes in the muscle fibers, with little or no alteration in the anterior horn cells.

The electromyogram in infantile muscular dystrophy is rather typical, as demonstrated by the following case.

CASE 11.—A 6-week-old female infant lay motionless and flaccid on the examining table. Respirations appeared to be normal. Stimulation of the peroneal nerve produced a brisk response. However, the contractions were not as strong as are usually seen. The mother stated that the intrauterine movements of the fetus had been very weak. At birth the child was flaccid and unable to move the extremities. On the date of the electromyogram the patient weighed 9 lb. 4 oz. (4,196 gm.). The electromyogram included examination of the right deltoid, and the left extensors and paraspinal muscles at the midthoracic and lumbar regions, the tibialis anterior, and the gastrocnemius, and revealed no spontaneous denervation activity and no polyphasic motor units. During reflex stimulation very small motor units, up to 40μv., were recorded. Although the motor units were small, it was also evident that their quantity was reduced, for they were somewhat hard to find. When localized, they were found to resemble infantile activity, except that they were actually innervated. The small reflex potentials were sus-

tained only briefly. No positive sharp waves were recorded.

Comment.—The absence of denervation activity and the very tiny motor units generated during voluntary efforts confirmed the diagnosis of typical infantile muscular dystrophy, as reported by Marinacci in 1956.[10] However, I have seen one infant in whom there was a combination of both denervation activity and very small motor units, denoting that the two systems, muscular and lower motor neuron, were simultaneously degenerating. This combination has also been observed in two adult patients who had muscular dystrophy and lower motor neuron disease simultaneously in progress. Therefore, the uses of electromyography can be applied to the diagnosis of so-called Oppenheim's disease to determine whether it belongs to the dystrophies or to the neuropathies. In the case of Werdnig-Hoffmann disease, the electromyographic findings suggest that the lower motor neuron has failed to develop, for possibly regressive changes have overtaken the development before it was completed.

In conclusion, it is necessary to state that, although the electromyogram can differentiate myopathies and neuropathies, some exceptions do occur. It is possible to distinguish between individual cases of amyotonia congenita (Oppenheim's disease), that is, whether they are the result of muscular dystrophy, peripheral neuropathy, or some disease of the lower motor neurons (Werdnig-Hoffmann disease). There remains a small group of infants who present a typical picture of amyotonia congenita but whose electromyogram is of no particular help because both the muscles and the nerves are electromyographically normal. This small group is therefore unclassifiable on this basis. This unclassified group can be explained only on the basis of a defect in the metabolism of the neuromuscular mechanism rather than as consequent to any structural changes in either the muscles or the nerves.

Aberrant Findings in Electromyograms of Normal Infants

Many infants were examined electromyographically because of other conditions, especially infants with cerebral palsy. In addition, five normal infants, ranging in age from 3 to 5 weeks, were specifically examined as a check in this investigation. In about 25% of these infants, a few isolated fibrillations were recorded in the interossei of the feet. However, this fibrillation seemed to be somewhat higher in voltage than the infantile type, the amplitude ranging up to 50μv., with a frequency from 2 to 5 per second. Occasionally positive sharp waves were also recorded. No polyphasic motor units were ever found. This situation can be explained in two ways: (1) A few muscle fibers are still in the process of innervation during the first few months of life, or (2) some fibers remain in an uninnervated state, as found in adults. The higher voltage of these potentials is apparently due to the fact that these few denervation fibers survive in the neighborhood of normal muscle elements, which help them to survive to a greater degree of maturity. This survival of denervated muscle fibers is seen rather frequently in clinical work. For example, I have recorded fibrillation of denervation in a patient, aged 64, with partial birth Duchenne-Erb paralysis. Apparently, the normally innervated muscle fibers in the neighborhood contribute to their survival. This is not the case, of course, in instances in which the lesion is complete.

Incidental Subclinical Electromyographic Findings in Adults

In the course of an electromyographic examination undertaken for other conditions, such as nerve injury and herniated intervertebral disk, one not infrequently finds subclinical electromyographic findings. Occasionally there is elicited an isolated denervation potential without polyphasic motor units. This strongly suggests that some isolated muscle fibers were never innervated

during intrauterine life. Also, one finds that in about 1 in 200 cases, high-frequency positive sharp waves are produced by needle stimulation. These sharp waves are of two types: (1) the positive short-lived sharp wave of denervation, which appears only during mechanical stimulation of the needle electrode, and (2) those which have a much higher frequency and have excursions similar to those found in myotonia. These two types of high-frequency discharges are found diffusely and are not accompanied by denervation or polyphasic motor units, the motor units generated being normal. This observation suggests that the nerve has only one control of the muscle in these cases, that is, trophic control; but the control over the excitable contractile mechanism is missing, as occurs in denervated muscle. In short, the contractile mechanism of the muscle fibers is not under the control of the nerve, remaining in its primitive, inherent state in this respect. Occasionally in these cases a single muscle fiber is observed to have identical high-frequency discharges with excursions, as occur in myotonia. Many of the patients may therefore be experiencing a borderline or subclinical myotonia.

Summary

The electromyogram has become a valuable aid in the diagnosis of neuromuscular diseases. This has been accomplished by contributing to an understanding of the normal dynamics of the neuromuscular function. This study points out that the total picture of the neuromuscular function must include the development from its embryonic status to its fully mature behavior. Dysfunction of the neuromuscular mechanism may therefore result from either of two etiological factors: (1) any interference in its embryonic development, and (2) a reversion of the normal mature neuromuscular activity to its infantile state, resulting from disease or injury of the lower motor neuron (neuropathies) or a disease of the muscle itself (myopathies). The embryonic development of the neuromuscular mechanism whose significance has not been fully appreciated to date is therefore the key to one's understanding of neuromuscular physiology. To trace the transformation of this activity during its course of development from embryonic life to maturity and its reversion to infantile state after interruption of the lower motor neuron path is the primary purpose of this investigation.

In order to investigate this phenomenon, a series of electromyograms were made in cases of (1) premature infants, (2) severe degrees of spina bifida in which the lumbosacral nerve roots have failed to innervate the corresponding muscle groups, (3) congenital failure of development of the lower motor neurons, (4) infantile neuropathies, (5) the myopathies in early life, (6) and instances of residual infantile activity still evident in children and adults. These observations revealed the following pertinent facts: 1. At the sixth month of intrauterine life there remain about 20% of the muscle fibers to be innervated. At the time of birth no more than 5%, on the average, have not yet received their nerve supply. At the end of four months from birth practically all the muscle fibers have been innervated. As is to be anticipated from what has been said about the gradient of innervation, the fibers yet to receive their nerve supply in the early months of life are largely in the lower extremities, especially in the intrinsic muscles of the feet. 2. Prior to their innervation, this group of muscle fibers possess an inherent tendency to fibrillation and are hyperirritable to mechanical stimulation which results in fibrillation and positive sharp wave activity. 3. This same type of preinnervation activity can also be elicited from the muscles affected by infantile muscular atrophy and the muscles of the lower extremities whose complete innervation has been prevented by meningomyelocele. 4. The preinnervation independent spontaneous activity recorded from the above-observed conditions proves that muscle fibers fibrillate in intrauterine life before they are innervated. 5. Preinnervation ac-

tivity is essentially the same in character as is denervation activity incident to lower motor neuron diseases and neuropathies. The chief difference lies in the fact that waves of the former are very much smaller in size and there is no evidence of demyelination to be found. 6. This observation suggests that neurotization and myelination (maturation) take place simultaneously during intrauterine life. This differs from peripheral nerve regeneration in that myelination follows neurotization. 7. In embryonic life the gradient development of the neuromuscular mechanism progresses from the neck to the pelvic girdle, then from the proximal to the distal portion of the extremities, and, ultimately, to the interossei of the feet. 8. The fusion of the sheath of Schwann with the sarcolemma therefore seems to be integrated with the fundamental dynamics of voluntary motor activity. 9. The fusion of these two elements is signalized by the cessation of all inherent spontaneous independent activity (fibrillation), as well as the excitability of the sarcolemma (hyperirritability). 10. By this fusion the individual muscle fibers no longer fibrillate but become wholly dependent on their motor nerve supply. In addition to supplying the trophic effect of the muscle, the motor nerve also suppresses spontaneous excitability (hyperirritability) of the sarcolemma. 11. The muscle regains its inherent fibrillation (twitching) and the spontaneous excitability of the sarcolemma when lower motor neuron disease or neuropathy again separate the muscle from the nerve. This is to say, the muscle reverts to its preinnervation or infantile type of activity. 12. The dynamics of myotonia apparently become manifest whenever the spontaneous excitation of the sarcolemma alone is freed from the suppressing effect of its nerve, the trophic effect of the nerve still being intact. 13. Residuals of preinnervation infantile activity can still be detected in some adults, as well as in children. The detection of subclinical infantile activity in later life may be the basis for subsequent development of diseases of the lower motor neuron (spinal muscular atrophy) and/or myopathies. 14. The residuals of this type of infantile activity persisting into life are of clinical significance, for such activity may be misinterpreted as a true neuromuscular disorder. 15. Because one can now recognize a specific difference between preinnervation, or infantile, activity and denervation activity resulting from acquired lower motor neuron lesions, the electromyogram can be used to distinguish lesions which occurred during intrauterine life from those occurring during or after birth.

The essential clue to the dynamics of neuromuscular disease may be expressed as follows: In this group of disorders mature neuromuscular activity reverts to immature preinnervation or infantile activity, and this activity is characterized by an inherent independent spontaneous fibrillation and hyperirritability (positive sharp waves).

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Effects of Lysergic Acid Diethylamide (LSD) on Cortical Sensory Evoked Potentials in the Cat

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Introduction

Several authors have reported the effects of lysergic acid diethylamide (LSD) on evoked potentials in primary sensory pathways. The areas studied were retina,[2] lateral geniculate body,[8] and visual,[9,14,18] auditory,[14,18] and somatic cortex.[14] There is incomplete agreement on the effects of LSD on visual and auditory cortex. Purpura [14] found facilitation of visual cortical potentials with small doses, whereas Evarts [8] found no significant effect with very large doses. Rovetta [18] used LSD topically and intravenously in small doses and reported an absence of effect on both visual and auditory potentials. Large doses of the drug have been used infrequently.

Numerous authors have described the effects of LSD on the electrocorticogram of several species of animals.* There is a great variation in the dose reported to produce a significant change in frequency and amplitude, as well as disagreement regarding the character of the changes.

The current study was designed to investigate the effects of LSD on cortical visual, auditory, and somatic evoked potentials and also to correlate these observations with the electrocorticogram by recording simultaneously with a cathode-ray oscilloscope (CRO) and an ink-writing oscillograph. Finally, an attempt was made to determine the minimal change in evoked potentials indicative of a drug effect.

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* References 3, 4, 7, 8, 10, 11, 16, 19, 20.

Methods

A total of 89 cats were used in this study. Sensory evoked potentials were studied in 39 cats which received LSD one or more times. The data from 27 were analyzed in detail and appear in the text.

Twenty animals were anesthetized with ether, then paralyzed with succinylcholine after the surgical procedures (Anectinized animals). Skin edges and pressure points were infiltrated with 0.5% procaine hydrochloride. Electrical recording was begun no less than two hours following cessation of ether anesthesia. The initial paralyzing dose of succinylcholine chloride was 20 mg., followed by 20-mg. supplements as required to prevent spontaneous movement. The animals were ventilated with a Marshall respirator.

Seven cats were anesthetized with pentobarbital sodium, 30 mg/kg., injected intraperitoneally, and additional intravenous injections were given as required to produce moderately deep anesthesia. Most of the animals were artificially ventilated to obviate any possibility of hypoxia.

Visual stimulation was produced by a small sealed bulb which delivered a narrow beam of light for 10 msec. to the eye contralateral to the recording electrode. Clicks from a loud-speaker mounted near the animal's head were used for auditory stimulation. Tactile stimulation was produced by a Goodman Industries "vibrator," mounted over a pad of the contralateral forefoot. All three sources of stimulation were operated by Tektronix pulse generators and wave-form generators with variable delays. In most experiments the three stimuli were delivered simultaneously at 2.5 second intervals.

A bank of 10 electrodes was used for recording from the cortex. The electrodes were spring-mounted, cylindrical, silver electrodes with a tip diameter of approximately 1 mm. The primary cortical area of each sensory modality was explored for a maximum response in every experiment. Monopolar recording was used with the indifferent electrode on the head holder or on bone surrounding the craniectomy.

Two methods of recording were used: The output was led (1) differentially into Tektronix preamplifiers, displayed on a Dumont dual-beam oscilloscope, and photographed with a Grass camera, and (2) into a Grass eight-channel electroencephalograph through a panel designed for rapid switching into the CRO of information appearing on any two channels of the electroencephalograph. Because none of the stimulus sources produced an electrical artifact, a fraction of each stimulus, with a variable amplitude control, was led directly into the CRO for more accurate observations of latency.

In a majority of the preparations, a "well" was constructed from the skin flaps following the craniectomy. Before retracting the dura, or immediately afterward, this was filled with warm liquid petrolatum U. S. P. (mineral oil) and changed periodically. In the remaining animals liquid petrolatum was placed on the cortex as required to prevent drying.

The rectal temperature was measured with a thermometer and recorded at hourly intervals. Body temperature was maintained with heat lamps or a heating pad.

The LSD used was the Sandoz Pharmaceuticals product "LSD-25 pure substance." This was dissolved in distilled water and administered through a catheter in the femoral vein. Initially, the drug was given within one hour of preparation, but subsequent experiments proved that solutions refrigerated for three days showed no diminution in effect. On the basis of several injections of distilled water, the volume of injection was found to be critical. A single injection of 8 ml. produced profound changes in the electrocorticogram, and occasional electrical silence for brief periods of time. Injections of 3 and 4 ml. produced no detectable effect. Therefore, the maximum volume of drug injection used was 2.5 ml.

LSD was given at eight dose levels, from 0.025 to 4.0 mg/kg.

Evoked potential amplitudes were analyzed in two ways. From the EEG records the amplitudes of 15 consecutive potentials were measured during the preinjection period and the mean amplitude calculated. Then similar measurements were made at numerous postinjection times. In addition, films of the CRO traces were projected onto graph paper in a microfilm reader, and the peak amplitudes were measured.

For illustrative purposes five consecutive traces from the CRO were superimposed on film at frequent times during each experiment.

The analysis of the electrocorticogram was based on the records of 80 injections in 48 animals. Each record was analyzed during the control period and several times after injection. Estimates of changes in frequency and amplitude were made by visual inspection and confirmed by measurements. Frequency changes in the electrocorticogram of 10 per second and amplitude changes of 50μv. following LSD were recorded as possible drug effects.

Results

Effects of Multiple Sensory Stimulation on Evoked Potentials

The recording loci of the three cortical evoked potentials are shown in Figure 1. The map of the cortical surface is representative of the animals used in this study; but, because of variations in the sulcal pattern of the cat's cortex, precise localization of electrode placement is not possible in this Figure. Most of these points of maximum response fall within the limits of the

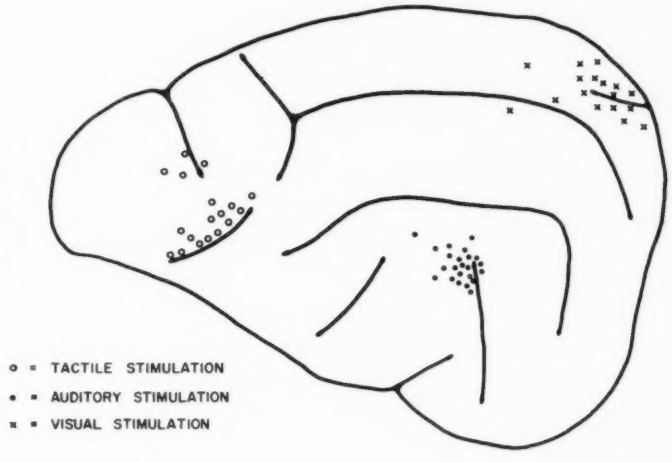


Fig. 1.—Cortical points of maximum response to sensory stimulation. Most of the recording points are within the primary area of each sensory modality as illustrated by Rose and Woolsey.

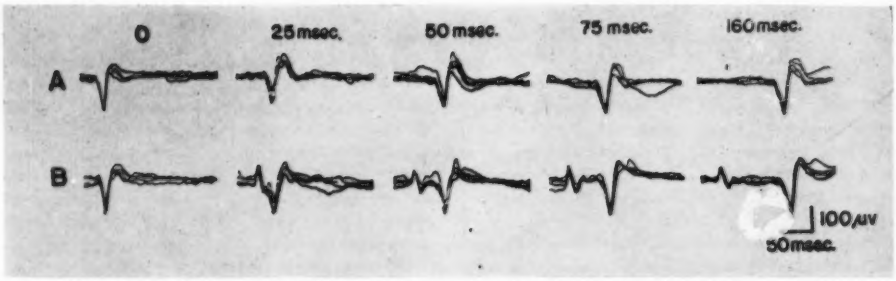


Fig. 2 (Cat 52).—Pentobarbital. Responses to click and tactile stimulation are recorded at the same point in primary somatic cortex. *A*, tactile stimulation; *B*, tactile and auditory stimulation. Auditory stimulation precedes tactile stimulation at time intervals indicated at the top of the Figure.

primary sensory areas as illustrated by Rose and Woolsey.[17]

The area of cortex responding to a single modality of stimulation varied greatly among animals, and this was particularly true of auditory stimulation. Marshall et al.[13] demonstrated distinct potential changes in primary auditory cortex in response to visual stimuli, but found no evidence of interaction between these potentials and auditory evoked potentials. The possibility of an interaction of diverse sensory stimuli at the cortical level has been investigated by Amassian,[1] who found in the cat, under chloralose anesthesia, blocking interaction among volleys from visual, somatic, and auditory receptors in the anterior lateral gyrus, and by Buser,[6] who found points in the association cortex responsive to auditory, vestibular, and somatic stimuli. However, Buser found that there was occasional facilitation of a response by stimulation of a different sensory modality.

Because all three stimuli were usually delivered simultaneously in the present study, it was important to determine whether an interaction among stimuli was present. Each primary area was examined with all three stimuli in succession. A response to clicks was seen occasionally in both primary

TABLE 1.—*Effect of LSD on the Electrocorticogram*
Succinylcholine (Anectine)

LSD Mg/Kg.	No. of Injections	No. of Effects	Volt. Incr.	Volt. Decr.	Freq. Incr.	Freq. Decr.	Sp. *	E. S. †
			First Injection					
0.025	1	0						
0.05	6	2	1	0	0	2	1	0
0.1	3	1				1	1	
0.25	4	1	0	1	0	0	0	0
0.5	2	2	1	0	0	2	1	0
1.0	8	8	4	4	0	8	0	4
2.0	4	4	1	0	0	4	1	0
4.0	2	2	1	1	0	1	0	1
			Second Injection					
0.025	1	0						
0.05	2	0						
0.1	4	1	0	0	0	1	0	0
0.25	1	1	1	0	0	0	0	0
0.5	5	2	0	2	1	1	0	1
1.0	3	3	0	0	0	3	1	0
2.0	3	2	0	2	0	1	0	1
Totals	49	29	9	10	1	24	5	7

* Sp. = spindling.
† E. S. = electrical silence.

visual and somatic cortex. Tactile stimulation rarely produced a response in auditory cortex, and after light flash there was never an evoked potential in either auditory or somatic cortex. In Figure 2 a small auditory evoked potential is recorded in primary somatic cortex. When the two stimuli were delivered simultaneously, the auditory response was obscured by the somatic evoked potential, but the amplitude of the latter was unchanged. When auditory stimulation preceded tactile stimulation at several time intervals, up to 160 msec., again there was no evidence of either inhibition or facilitation of the latter. Despite this observation, recording points used for the drug study were those responsive to a single modality of stimulation.

Effects of LSD on the Electrocorticogram

Tables 1 and 2 show the incidence of changes in frequency and amplitude of the electrocorticogram following LSD. Anesthetized and Anectinized animals have been considered separately in order to assess the effects of pentobarbital. Table 1 shows that all initial injections of 0.5 mg/kg. in Anectinized animals produced alterations of frequency or amplitude or both. Obliteration of the electrocorticogram was produced frequently by large doses. Table 2 indicates that the results are similar in the pentobarbitalized animals except that effects occurred more frequently at 0.25 mg/kg. However, the number of injections of this dose was insufficient for these differences to be significant. A difference in effect between the two preparations is also suggested by the number of times the electrocorticogram was obliterated in the two series. Following 5 of 30 injections there was electrical silence in the Anectinized preparations, whereas this occurred 8 of 17 times in the anesthetized animals.

In most of the Anectinized animals there was a low-voltage, fast pattern of cortical activity prior to injection, and in all animals, except one in which some change occurred after injection, there was significant slowing. In contrast, the cortical activity of the anesthetized animals was slow during the preinjection period, but the drug produced no further change in frequency unless there was progression to electrical silence.

In many experiments changes were not uniform throughout the cortex. Frequently, the visual cortex did not exhibit the 20-30 per second activity seen in auditory and somatic cortex, and the amplitude was often lower. This resulted in less evidence of change in visual cortical activity with small doses of drug. However, when profound effects were produced by very large doses,

TABLE 2.—*Effect of LSD on the Electrocorticogram*
Pentobarbital

LSD Mg/Kg.	No. of Injections	No. of Effects	Volt. Incr.	Volt. Decr.	Freq. Incr.	Freq. Decr.	E. S.
			First Injection				
0.025	1	0					
0.25	7	5	0	5	0	2	2
0.5	5	4	0	4	0	2	2
1.0	4	4	0	4	0	3	3
2.0	1	1	0	0	0	1	1
			Second Injection				
0.05	2	1	0	1	0	0	0
0.1	1	1	0	1	0	0	0
0.25	1	1	0	1	0	1	1
0.5	5	3	0	3	0	1	1
1.0	3	2	0	2	0	1	1
2.0	1	0					
Totals	31	22	0	21	0	11	11

E. S. = electrical silence.

all areas were equally affected. Spindles of 8 to 12 per second were seen occasionally following LSD in the Anectinized animals.

Following a second injection, 20 minutes to 3 hours after the initial dose, fewer effects were seen in both anesthetized and Anectinized animals, and the extent of change was less. Electrical silence occurred 5 times, as opposed to 12 times after the initial injection.

Effects of LSD on Evoked Potentials in Anectinized Animals

In the initial experiments LSD was given in doses of 0.025 to 0.2 mg/kg. in an attempt to determine the minimum quantity required to produce a consistent change in the amplitude of the evoked potential. Table 3 and Table 4, respectively, show the postinjection mean amplitudes of auditory and somatic evoked potentials expressed as percentages of preinjection mean amplitudes. An increase, no change, and an occasional decrease in amplitude are observed. Neither Table suggests a relation of dose to effect, since amplitude changes following 0.025 and 0.2 mg/kg. are about the same.

TABLE 3.—*Effect of Relatively Small Doses of LSD on Cortical Auditory Evoked Potentials* *
Succinylcholine (Anectine)

Animal No.	LSD Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
37	0.025	140	125		115	100	95
37 †	0.025	105	115	115		110	100
21	0.05	110		110			
23	0.05	125			100		
26	0.05	125		115			
28	0.05	110		115	120		110
33	0.05	100	110	110	110	100	110
33 †	0.05	125	115	115		110	100
24	0.1	100				100	
32	0.1	110	130		110		105
21 †	0.1	105		100			
28 †	0.1	95		105		75	65
32 †	0.1	125		145		115	105
28 ‡	0.1	100		100			110
33 ‡	0.1	120	115	110		105	110
33 §	0.1	100		105	80		
24 †	0.2	95				95	
21 ‡	0.2	100		100			

* Postinjection mean amplitudes are expressed as percentages of preinjection mean amplitudes.

In those preparations which received multiple injections, †, second injection; ‡, third injection, and §, fourth injection.

TABLE 4.—*Effect of Relatively Small Doses of LSD on Cortical Somatic Evoked Potentials*
Succinylcholine (Anectine)

Animal No.	LSD Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
37	0.025	100	100		100	105	85
37 †	0.025	135	120		155	130	165
26	0.05	120		90	100	125	
28	0.05	100		105	100		
33	0.05	110	85	90	90	95	115
26 †	0.05	120		100			
33 †	0.05	100	100	100		85	75
37 ‡	0.05	140	130		125	155	140
37 §	0.05	110			105	85	100
32	0.1	150	160		130	135	90
28 †	0.1	85		80		75	45
33 ‡	0.1	120	100	120		105	100
33 §	0.1	105		110	85		

* Postinjection mean amplitudes are expressed as percentages of preinjection mean amplitudes.

† Second injection.

‡ Third injection.

§ Fourth injection.

In the animal represented by Figure 3, injections of 0.05 and 0.1 mg/kg. of LSD were given two hours apart. There was no change following either injection, but between doses there had been a gradual decline in amplitude of both auditory and somatic potentials. Spontaneous cortical activity was unchanged.

The change in mean amplitude of evoked potentials following administration of a drug can be significant only in relation to spontaneous fluctuations in amplitude which might occur at the same time. Therefore, it is necessary to determine the actual variability in a preparation before ascribing to the drug changes which occur during the postinjection period. In general, evoked potentials are most consistent with minimal background activity, and when the background is obliterated, there may be no detectable amplitude differences for several minutes. In contrast, when the amplitude of spontaneous cortical activity is 100μv. or more, evoked potentials may vary so greatly in configuration and amplitude that accurate measurement is difficult.

Because of the variability within series of evoked potentials and the inconsistent changes in mean amplitude following LSD, a comparison was made of the mean ampli-

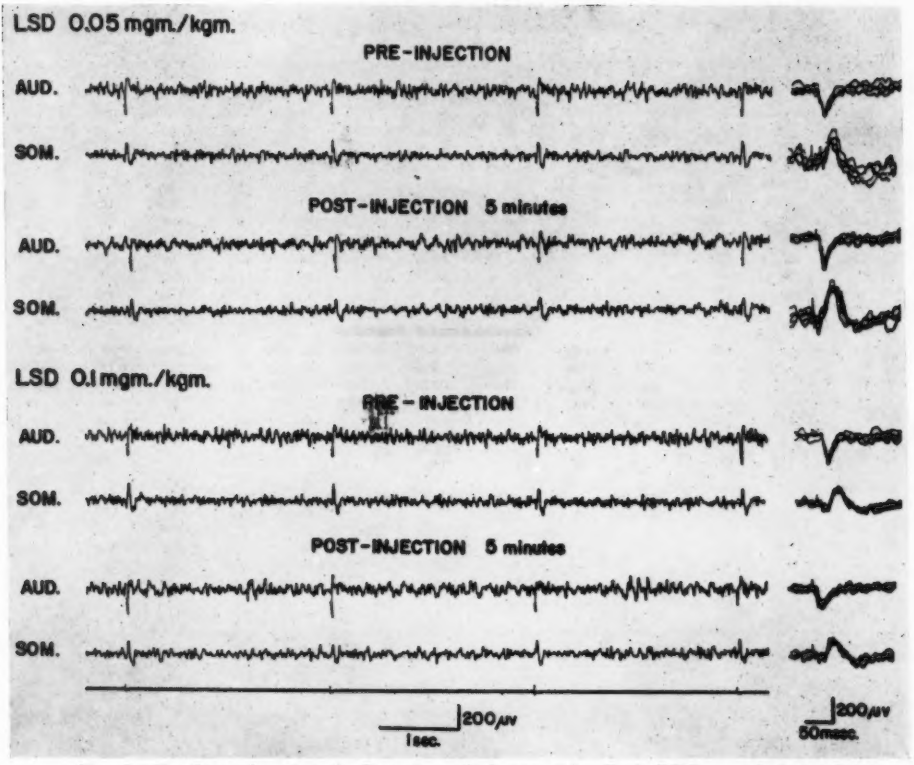


Fig. 3 (Cat 26).—Anectinized. Somatic evoked potentials. Each EEG record shows four evoked potentials at 2.5-sec. intervals. To the right of each EEG record are five single-sweep superimposed CRO traces recorded at approximately the same time as the corresponding EEG records.

A, LSD 0.05 mg/kg.; *B*, LSD 0.05 mg/kg. Description in text. Calibration and time line for EEG on left, for CRO on right.

tudes obtained during a one-hour period prior to injection and the mean amplitudes during the first hour after injection. These data are presented in Table 5. In each animal the three stimuli were delivered simultaneously and continuously throughout the experiment. After satisfactory evoked potentials were obtained, the control period was begun, at time zero; 15 consecutive potentials were measured and the mean amplitude calculated. Subsequent mean amplitudes were determined at the prearranged times indicated in the Table. This portion of the experiment was terminated at the end of one hour. The same procedure was then repeated except that LSD was injected immediately after measurement of evoked potentials at zero time. Mean amplitudes are expressed as percentages of control mean amplitudes obtained at the beginning of each time period.

The data in Table 5 show marked variability in evoked potential amplitudes during the preinjection period and following large doses of LSD. The changes are inconsistent. An increase or a decrease in amplitude appears to occur randomly, but the magnitude of change, in both directions, is slightly greater in some animals than during the control period.

Figure 4 shows records obtained within one minute during a control period. In the lower record, the background activity has decreased in amplitude and increased in

TABLE 5.—*Comparison of the Spontaneous Variability in Amplitude of Cortical Evoked Potentials with the Variability Following Administration of Large Doses of LSD* *

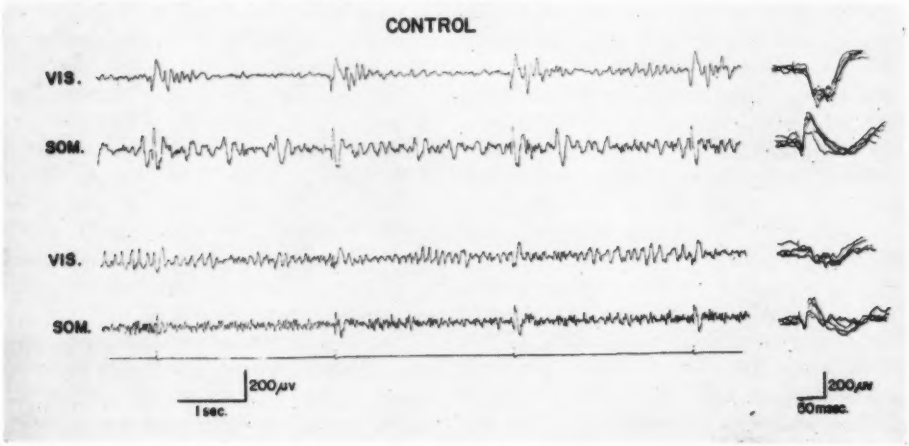
Animal No.	Preinjection, Min. 5	10	20	30	60	LSD Mg/Kg.	Postinjection, Min. 2	5	10	20	30	60
Auditory Evoked Potential												
40		95	85	85	80	1.0	135		130	110		
41		110	90	95		1.0	105	100	95	100	105	115
38		90	85		90	2.0	155	180	190	180	180	185
39		100	105	110	115	2.0	120	150	90	50		90
42	115	125		130	115	2.0	115	125	110		115	105
45	120	90		80	90	2.0	115	125	130	130	120	110
46	120	105	100	130	115	2.0	125		135		100	
Somatic Evoked Potential												
40		100		80	80	1.0	90	100		100	110	125
41		125	100	120		1.0	105	75	100	120	120	115
38			110	115	120	2.0	140	140	140	150	150	155
39		100	100	105	100	2.0	100	115	120	80		115
42	105	100		125	125	2.0	145	140	135		135	140
45	115	105		100	95	2.0	105	110	115	115	120	115
46	120	105	100	130	115	2.0	100		110		90	
Visual Evoked Potential												
40		80	60	65	50	1.0	[illegible]	140		130	125	145
41		105	75	75		1.0	90	60	70	95	80	100
38			95	90	90	2.0	[illegible]	100	105	120	100	125
39		90	85	90	85	2.0	110	135	40	30		80
42	95	150		140	110	2.0	140	100	85		140	150
46	100	115	100	85	100	2.0	105		70			

* Postinjection mean amplitudes are expressed as percentages of preinjection mean amplitudes.

frequency, and there has been a marked reduction in the amplitude of the visual evoked potentials.

The information in Figure 5 is taken from the same animal as that in Figure 4. Following 1.0 mg/kg. of LSD there is decreased amplitude, then increased amplitude and recovery of both visual and auditory potentials. However, the change in the visual potential is only slightly greater than the natural variation in amplitude seen in Figure 4.

Fig. 4 (Cat 39).—Anectinized. The upper EEG channel in each pair is the record from visual cortex; the lower channel, from somatic cortex, and the lowermost channel, stimulus artifact. The two sets of records are obtained within one minute during the preinjection period. Note the marked change in amplitude of visual potentials.



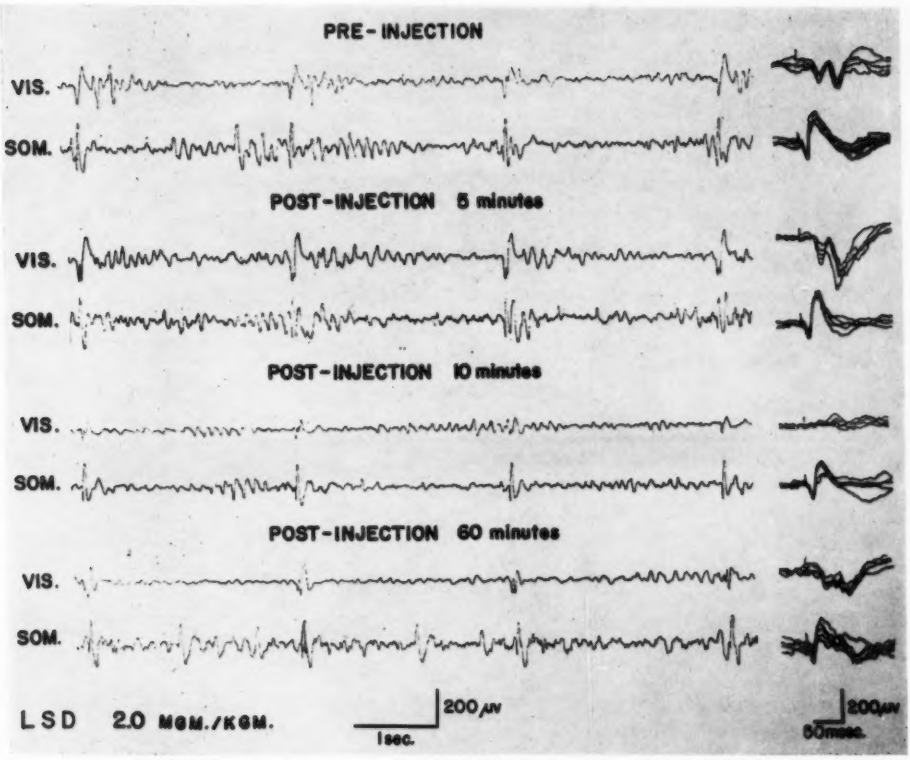


Fig. 5 (Cat 39).—Anectinized. The upper EEG channel in each pair is the record from visual cortex; the lower channel, from somatic cortex. LSD 2.0 mg/kg. Note that changes in the amplitude of visual evoked potentials are only slightly greater than in Figure 5.

Effects of LSD on Evoked Potentials in Animals Anesthetized with Pentobarbital

Auditory and somatic evoked potentials were studied in anesthetized animals following 17 injections of 0.2 to 4.0 mg/kg. of LSD. Amplitude changes were no more significant in these animals than in the Anectinized cats.

Figure 6 illustrates the constant amplitude of evoked potentials seen in deep barbiturate anesthesia when the spontaneous activity of the cortex has been reduced.

Following 1.0 mg/kg. there is a 50% decrease and recovery of somatic potentials. After a second injection, of 2.0 mg/kg., two hours later, there is doubtful change in amplitude.

Comment

The effects of LSD on evoked potentials in the primary sensory cortex of the cat were inconsistent. Small doses had no significant effect on auditory evoked potentials, although the number of times there was an increase in mean amplitude exceeded the number of times there was no change or a decrease. Minimal differences existed in the responses of auditory and somatic cortex. Following 1.0 and 2.0 mg/kg. more animals showed an increase in amplitude of both auditory and somatic potentials than following small doses; but when these data were compared with the spontaneous variability in amplitude prior to injection, it was apparent that a significant change,

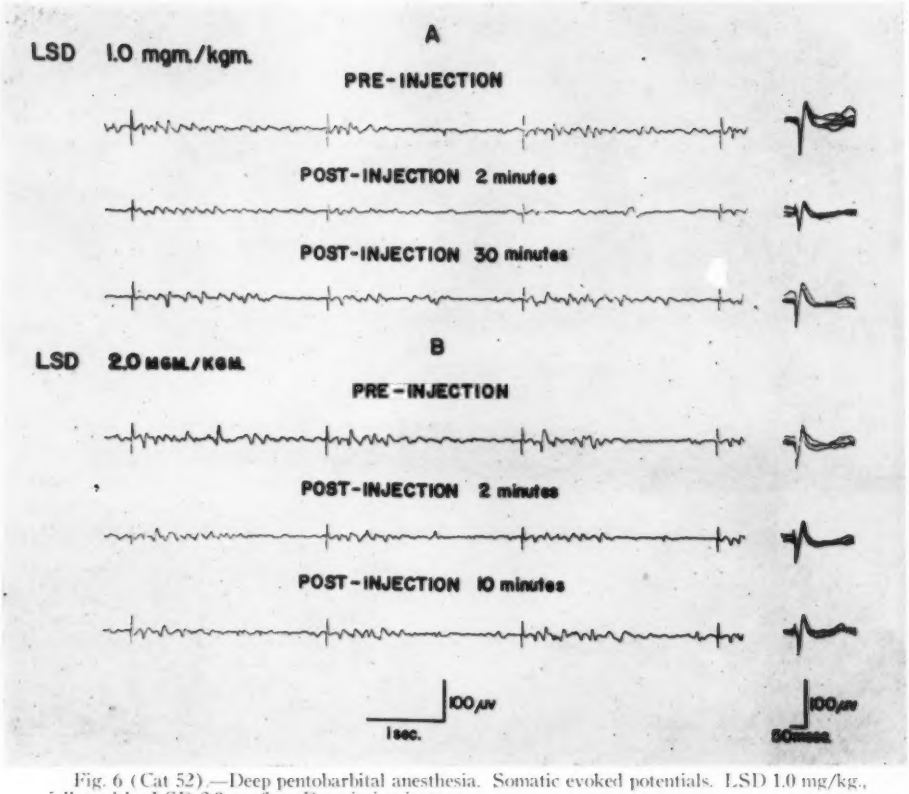


Fig. 6 (Cat 52).—Deep pentobarbital anesthesia. Somatic evoked potentials. LSD 1.0 mg/kg., followed by LSD 2.0 mg/kg. Description in text.

which might have been attributed to the drug, occurred no more than two times. Effects on visual evoked potentials were no more convincing, enhancement occurring as often as depression.

These results are in general agreement with those of Evarts,[8] who was unable to find a consistent change in the cortical response to submaximal stimulation of lateral geniculate radiation fibers with doses of LSD as large as 1 mg/kg. His experiments were performed in chronic unanesthetized preparations. In contrast, Purpura [14,15] found an increase of auditory, somatic, and visual evoked potentials following doses of 0.02-0.05 mg/kg. With slightly larger doses the auditory response was inhibited, but there was continued facilitation of the visual response. After 0.07-0.1 mg/kg. there was a decrease of all cortical evoked potentials. Purpura's animals were anesthetized with pentobarbital or ether, immobilized with succinylcholine, and allowed to recover from the anesthesia. Rovetta [18] gave LSD in doses as large as 0.04 mg/kg. and found no effect on auditory or visual potentials in the cortex. LSD applied topically to the cortex, also, was without effect, in contrast to mescaline, which produced a marked increase of visual evoked potentials.

Evarts [8] found that the quantity of LSD required to decrease the postsynaptic geniculate response in intact unanesthetized animals was 30 times the dose required to produce the same effect in animals anesthetized with pentobarbital. In the present study the results did not indicate that cor-

tical potentials were made more sensitive to LSD in the presence of pentobarbital. However, this finding is probably explained by the observations that cortical evoked potentials are quite resistant to the drug in all experimental situations, whereas synaptic transmission in the lateral geniculate is readily affected.

Multiple injections of LSD were no more effective in altering evoked potentials than was a single injection. This was true irrespective of whether subsequent injections contained the same or larger quantities of drug.

The effects of LSD on the spontaneous electrical activity of the cortex have been studied in the rat,[20] the rabbit,[7,16] the cat,[3,9,10,11,19] and the monkey.[4] Rinaldi and Himwich [16] found long-lasting alerting of the EEG of rabbits with 0.001-0.015 mg. and an opposite effect with 0.02 mg. or more. Bradley and Elkes [3] observed abolition of barbiturate spindling after 0.1-0.15 mg/kg. in cats, but in unanesthetized animals doses up to 0.3 mg/kg. produced no effect. This contrasts with the observations of Delay et al.,[7] who found that flattening of the electrocorticogram following LSD was prevented by pretreatment with barbiturates.

In the present investigation, 0.5 mg/kg. or more produced changes in cortical activity after 37 out of 46 injections, whereas doses of 0.1 mg/kg. or less were effective after 6 of 20 injections. These results indicate that small doses of LSD may produce changes in cortical activity, but 0.5 mg/kg. is required to produce consistent effects. Differences related to anesthesia were of doubtful significance.

One of the principal problems in this investigation was the determination of what constituted a significant drug effect. Previous reports on the effects of drugs on cortical evoked potentials have depended on visual inspection of graphs which plot amplitude against time during the postinjection period. Our experience casts doubt on the validity of these methods because of the spontaneous variability in evoked potential amplitude. It has been demonstrated in several figures in this report that apparently significant changes in amplitude occur over a wide dose range of LSD, and these changes are seen in the EEG records and the superimposed CRO traces. However, Figure 5 demonstrates the variability in amplitude encountered in untreated animals.

Analysis of the control data in Table 5 indicated that mean amplitude differences in evoked potentials were meaningless if not related to the variability occurring within each series analyzed. It has also been shown that when background activity was reduced under deep barbiturate anesthesia, fluctuations in amplitude were minimal. In this circumstance there were no changes in evoked potential amplitude following LSD.

The same problems obtain in analysis of drug effects on the electrocorticogram. Frequency and amplitude changes occur commonly with slight environmental changes. This has been emphasized by Bradley and Key [5] in their studies of the effect of drugs on thresholds for EEG arousal. In the present experiment it was recognized that many of the alterations in cortical activity which were attributed to LSD could have been produced by extraneous influences.

Summary and Conclusions

The effects of LSD on cortical potentials evoked by auditory, visual, and tactile stimulation were studied in the cat. Conclusions are based on detailed analyses of the data from 27 experiments. Succinylcholine-treated (Anectinized) animals and animals anesthetized with pentobarbital were used. Doses from 0.025 to 4.0 mg/kg. were administered intravenously. Evoked potentials were displayed on a cathode-ray oscilloscope, and the electrocorticogram was recorded with an ink-writing oscillograph. No significant change in amplitude of any of the three cortical potentials was noted with doses of 0.2 mg/kg. or less. When 1.0 mg/kg. or more was given, there appeared to be an increase in amplitude of auditory evoked potentials in some animals. However, when these data were compared with the varia-

bility in amplitude which occurred in the same animals during preinjection control periods, the changes observed following the injection of LSD did not appear significant. It was not possible to establish general criteria for ascertaining a significant drug effect because the natural variability in amplitude of evoked potentials dictated that each animal serve as its own control.

Changes in the electrocorticogram occurred in almost all animals following 0.5 mg/kg. of LSD. Effects were also observed with less consistency after smaller doses. The interpretation of drug effects on the electrocorticogram is subject to the same limitations applied to evaluation of evoked potentials.

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Effects of LSD on Cortex of Cat Correlated with Changes in Vital Signs

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Introduction

In a previous report[15] it was demonstrated that large doses of lysergic acid diethylamide (LSD) had no consistent effect on primary sensory evoked potentials in the cortex of the cat. However, in a recent publication Purpura[21] reported qualitative differences in the effect of LSD on cortical evoked potentials and postulated that these were due to anatomical differences in the termination of afferents in the cortex, some ending on soma and others on dendrites. Sensory afferents end primarily on the soma of cortical neurons.

In contrast, direct electrical stimulation of the cortex produces a predominantly surface-negative wave, which is generally considered to represent the activity of apical dendrites.[5,8,10] Furthermore, it is also thought to be a postsynaptic potential analogous to the postsynaptic potential of motoneurons in the spinal cord.[9] Also, anatomical evidence has been advanced to indicate that callosal fibers terminate primarily on dendrites or as free endings.[18]

The purposes of the present study were to investigate the effects of LSD on the direct response of the cortex and the transcallosal evoked potential and to correlate the effects on cortical activity with changes in the vital signs of the animal.

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Methods

The methods used for preparation of the animal and electrical recording were the same as those described in a previous report.[15]

The direct response of the cortex was obtained by stimulating the surface of the suprasylvian gyrus with bipolar electrodes made from fine strands of insulated steel wire. The interelectrode distance was 0.5 mm. or less. A monopolar recording electrode was positioned on the cortical surface approximately 2 mm. from the stimulating electrodes, and the indifferent electrode was placed on bone surrounding the craniectomy. The transcallosal evoked potential was recorded with a monopolar electrode on the suprasylvian gyrus in response to stimulation of an approximately symmetrical point on the contralateral suprasylvian gyrus.

Square-wave pulses 0.1 msec. in duration were used for cortical stimulation. The stimulus intensity varied from 2 to 8 volts.

The electrocardiogram was recorded on one channel of the Grass ink-writing oscillograph. The femoral artery was catheterized and the blood pressure measured with a Sanborn electromanometer and single-channel D. C. amplifier. Respiratory changes were determined by observation of the animal and by the respiratory excursions which were usually superimposed on the blood pressure records.

Detailed analysis of evoked potential amplitudes was performed in 26 animals, which received a total of 57 injections of LSD. Because it was often impossible to distinguish the shock artifact from the evoked potential in the EEG records, amplitude measurements were made from the cathode-ray oscilloscope (CRO) traces. Using a microfilm reader, 10 consecutive traces were projected onto graph paper, and the peak amplitudes were plotted and measured. The mean amplitude was calculated for each series of 10 traces during the control period and at numerous times after injection of LSD. The postinjection mean amplitudes are ex-

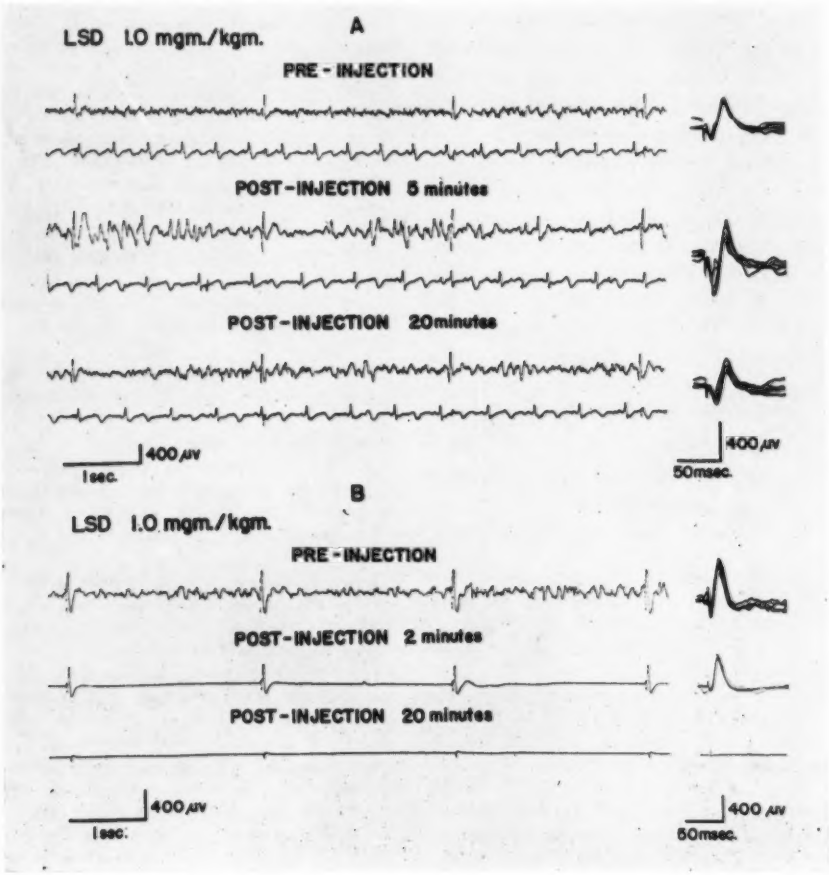
pressed as a percentage of the preinjection mean amplitude in each experiment.

Results

Description of Evoked Potentials

The direct response of the suprasylvian gyrus obtained in these experiments was primarily a surface-negative 20-40 msec. wave. Occasionally a small positive wave preceded the large negative wave, and usually there was a second positive wave, which in a few experiments was as large as the negative component. These findings are in agreement with the descriptions of Chang,[5] Bishop and Clare,[2] and Ochs.[19] Chang also identified a second negative wave, which appeared only with strong stimulation. In some of Chang's and Ochs' illustrations this second negative wave follows the initial

Fig. 1.—*A* (Cat 77): Succinylcholine-treated (Anectinized). LSD 1.0 mg/kg.
Each record shows four evoked potentials at 2.5 sec. intervals. To the right of each record are five single-sweep superimposed CRO traces recorded at approximately the same time as the corresponding EEG record. The top EEG channel of each pair records transcallosal evoked potentials; the lower channel, the EKG. Note preferential facilitation of positive wave after LSD.
Calibration 200μv. Time line 1 sec.
B (Cat 50): Anectinized. LSD 1.0 mg/kg.
Note preferential inhibition of the positive wave of transcallosal evoked potential prior to complete inhibition of cortical activity.
Calibration 200μv. Time line 50 msec.



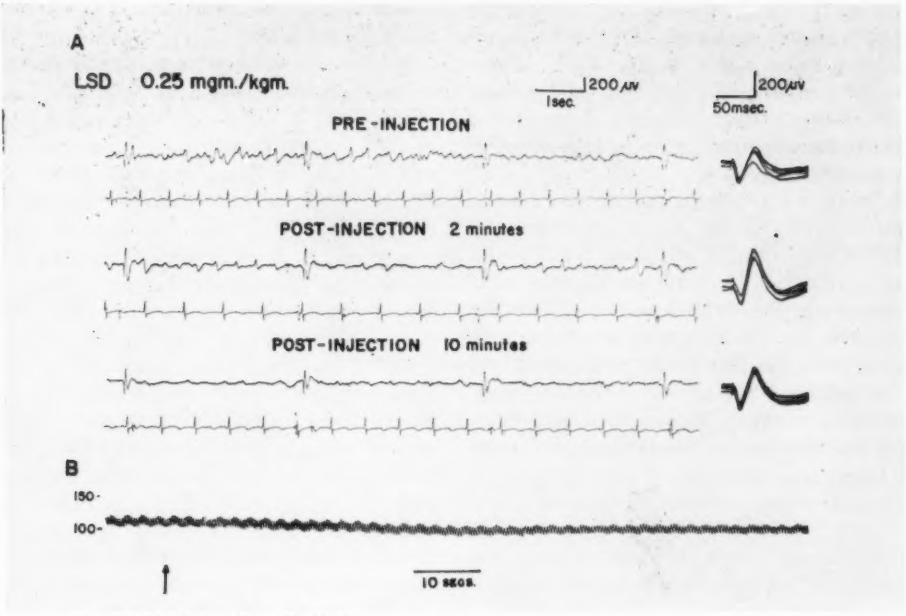


Fig. 2 (Cat 78).—Pentobarbital.

A, transcallosal evoked potentials. LSD 0.25 mg/kg. The lower channel of each EEG pair is the EKG. Description in text.

B, blood pressure record. The figures to the left indicate millimeters of mercury. The arrow indicates injection of LSD 0.25 mg/kg.

negativity without a return to isopotential. In Figure 5 of the present report, two negative peaks can be distinguished in the superimposed CRO traces. In this study interest was focused on the effects of LSD on the primary negative potential.

Transcallosal evoked potentials were recorded in suprasylvian, lateral, and ectosylvian gyri, but the largest and most consistent responses were obtained in the suprasylvian gyrus, a finding which corresponds with those of Chang.[6] Furthermore, the anterior suprasylvian gyrus gave more consistent evoked potentials than the middle or posterior segment, as was also noted by Peacock.[20] Observations on the configuration of the evoked potential in relation to the intensity of stimulation were also similar to those of Chang, i. e., a predominantly surface-negative response with liminal stimulation and a large positive wave with obliteration of the negative component with high stimulus intensities. Most of the evoked potentials used for this study were simple positive-negative responses of 30-50 msec., produced by submaximal stimulation.

Effects of LSD on Transcallosal Potentials

The effects of LSD on transcallosal evoked potentials were studied with doses of 0.2-3.0 mg/kg. In succinylcholine-treated (Anectinized) preparation the results were inconsistent. Doses of 0.5 mg/kg. of LSD had little effect, whereas 1.0 mg/kg. produced significantly varying effects in several animals. These results are illustrated in Figure 1. In *A*, after 1.0 mg/kg. of LSD, the amplitude of the negative component has increased slightly, but there has been preferential increase of the positive wave. Before injection the electrocorticogram showed the typical low-voltage fast activity seen in Anectinized preparations, but at the time of maximum increase of the evoked potentials, marked slowing and an increase in amplitude of the ECG have occurred. This results in greater amplitude variability

among the evoked potentials, which is manifested in this Figure by less precise superimposition of CRO traces. There is also marked bradycardia, which is still present 20 minutes after injection, at a time when the transcallosal potentials have returned to control amplitude.

In Figure 1*B*, from another preparation, injection of 1.0 mg/kg. of LSD has been followed by an equally marked, but opposite, effect. In this instance the negative component of the evoked potential has not changed, at a time when the spontaneous activity of the cortex has disappeared and the positive wave of the evoked potential has been markedly depressed. These observations, that the positive component is more affected in both increase and decrease of the transcallosal potential, are not confirmed in other experiments. In fact, after injections in two animals the negative wave was increased two- and threefold, and the positive wave was proportionately decreased.

When LSD was administered to animals under pentobarbital anesthesia, there was a consistent lack of effect on the amplitude of the transcallosal potentials with all doses. In only two instances was there a decrease of 50% or more, and in only one animal was there a significant increase. Figure 2 shows a 40% increase of evoked potentials two minutes after the injection of 0.25 mg/kg. of LSD in a deeply anesthetized animal. An increase of the negative component has occurred without change in the positive wave, the reverse of the effects observed in Figure 1. Figure 2*B* is the blood pressure record from this animal, with superimposed respiratory excursions. There has been a slight decrease in blood pressure, bradycardia, and some reduction in respiratory rate. All of these effects occurred less than one minute after injection. In contrast, Figure 3 shows abolition of the evoked potential, except for a small positive wave, after 1.0 mg/kg. of LSD. Spontaneous cor-

Fig. 3 (Cat 75).—Pentobarbital.

A, transcallosal evoked potential. LSD 1.0 mg/kg.

The lower channel of each EEG pair is the EKG. Note the marked bradycardia at the time of almost complete inhibition of transcallosal potential.

B, blood pressure record. One arrow: injection of LSD 1.0 mg/kg.; two arrows: respirator on. Note the marked arrhythmia. Further description in text.

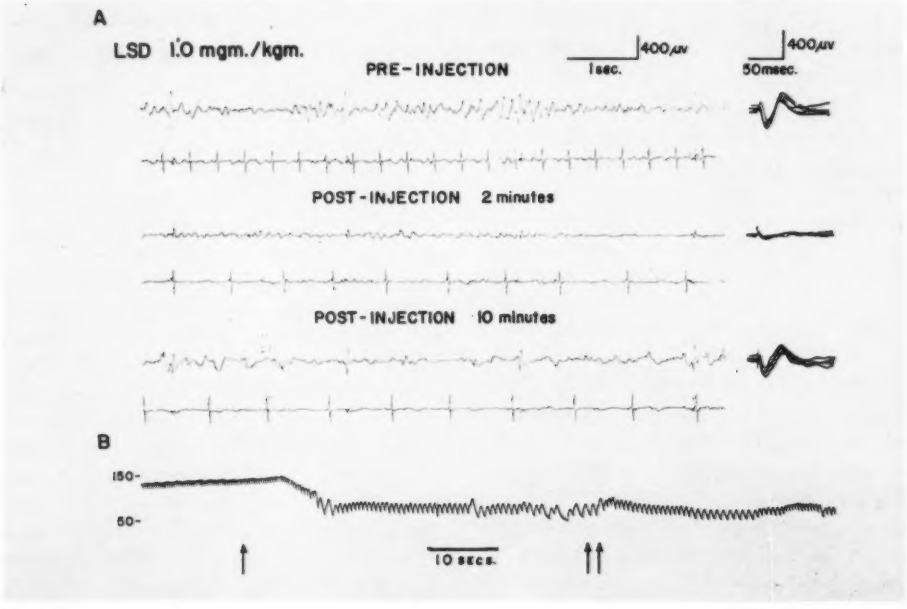


TABLE 1.—*Effect of LSD on the Transcallosal Evoked Potential* *
Succinylcholine (Anectine)

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
71	0.1	100	105	105		80	85
73	0.25	95	85	80	85		85
77	0.25	90	90	125	110		145
73 †	0.5	145	110	110	125		140
77 †	0.5	85	90	95	100		70
50	1.0	65	0		0		
76	1.0	95	70	70			
73 ‡	1.0	70	100	95	90		125
77 ‡	1.0	95	200	150	100		155
55	2.0	30	0		0		
73 §	3.0	55		50	100		
77 §	3.0	30	50	80	80		

* Postinjection mean amplitudes are expressed as the percentage of preinjection mean amplitudes.

In those preparations which received multiple injections, † indicates second injection; ‡, third injection, and §, fourth injection.

tical activity is still present, though greatly depressed. There is marked bradycardia and a profound fall in blood pressure, seen in *B*. Respiratory excursions are difficult to detect in this record, but the animal was observed to stop breathing within 10 seconds after the injection. Bradycardia was followed by cardiac arrhythmia, at which time mechanical ventilation was begun. Ten minutes after injection, at the time of recovery of evoked potentials, the blood pressure had approached the control level.

The effects of LSD on the transcallosal evoked potential are indicated in Tables 1 and 2.

TABLE 2.—*Effect of LSD on the Transcallosal Evoked Potential* *
Pentobarbital

Animal No.	LSD, Mg/Kg	Postinjection Times, Min. 2	5	10	20	30	60
70	0.25	110	85	75	85	60	
74	0.25	90	100	90	85		80
75	0.25	95	110	110	90		85
78	0.25	140	125	110	95		100
80	0.25	90	90				
74 †	0.5	65	90	100	100		70
75 †	0.5	105	90	100			110
78 †	0.5	100	110	105	100		100
80 †	0.5	100	60	140	115		
54 †	0.75	85	80	80	85		80
49	1.0	80	80	80		80	
49 †	1.0	110	125	100	60		65
74 ‡	1.0	105	100	120	130		100
75 ‡	1.0	20	70	115			80
78 ‡	1.0	85	110	110	110		110
80 ‡	1.0	95	110	85		75	
79	2.0	80	30	100		120	100
74 §	3.0	100	120	130	115		95
75 §	3.0	95	105	100		110	115
78 §	3.0	90	100	100	100		

* Postinjection mean amplitudes are expressed as the percentages of preinjection mean amplitudes.

† Second injection.

‡ Third injection.

§ Fourth injection.

Effects of LSD on the Direct Cortical Response

Effects on Amplitude.—The effects of LSD on the amplitude of the direct response were no more consistent than those observed on the transcallosal potentials. In Anectinized animals abolition of all cortical activity, with failure to recover, occurred in three animals, two of which received 0.5 mg/kg. of LSD. In two other preparations, which received 0.1 and 0.5 mg/kg., respectively, there was a gradual increase to two times the control amplitude at the end of an hour. These data are presented in Table 3. Figure 4 shows a slight increase in amplitude of the direct response, which undoubtedly is not significant. A slight but distinct bradycardia has occurred and also, in *B*, a transient increase in blood pressure. The excursions of the respirator are clearly seen on the blood-pressure tracing. In Figure 5 the amplitude of the direct response has gradually increased during the 60 minutes after injection. Also, there has

TABLE 3.—*Effect of LSD on the Direct Response of the Suprasylvian Gyrus* *
Succinylcholine (Anectine)

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
71 †	0.1	100	135	135		125	200
58	0.25	115	115	85		110	105
59	0.25	125	115	100	90		85
57	0.5	80	0			0	
63	0.5	115	165	170	165		225
57 †	0.5	60	0			0	
59 †	0.5	100	90	125	90		85
63 †	0.5	110	110	110	110		95
64	1.0	100	0			0	
71 ‡	1.0	90	90	75	100		95
63 ‡	2.0	85	120	115	110		85

* Postinjection mean amplitudes are expressed as the percentages of preinjection mean amplitudes.

† Second injection.

‡ Third injection.

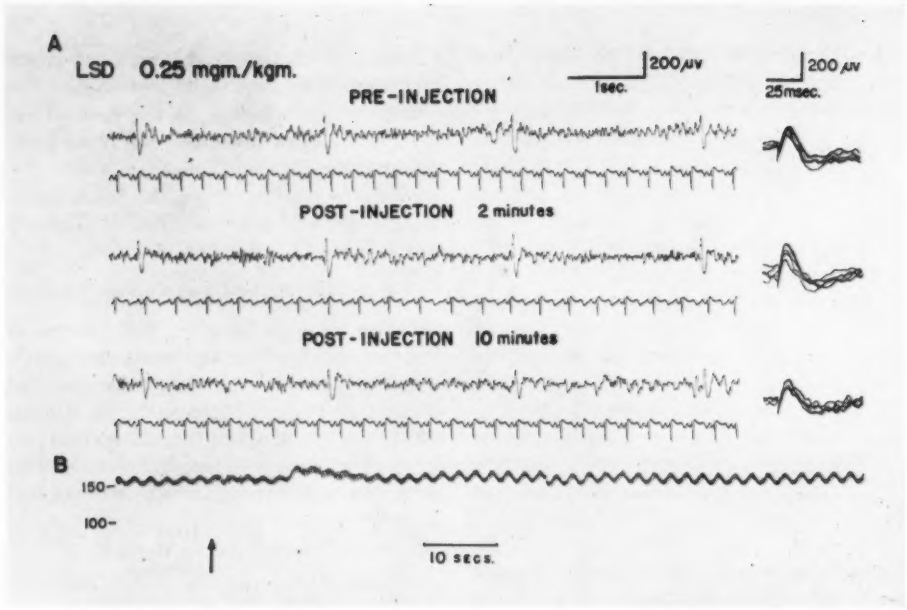
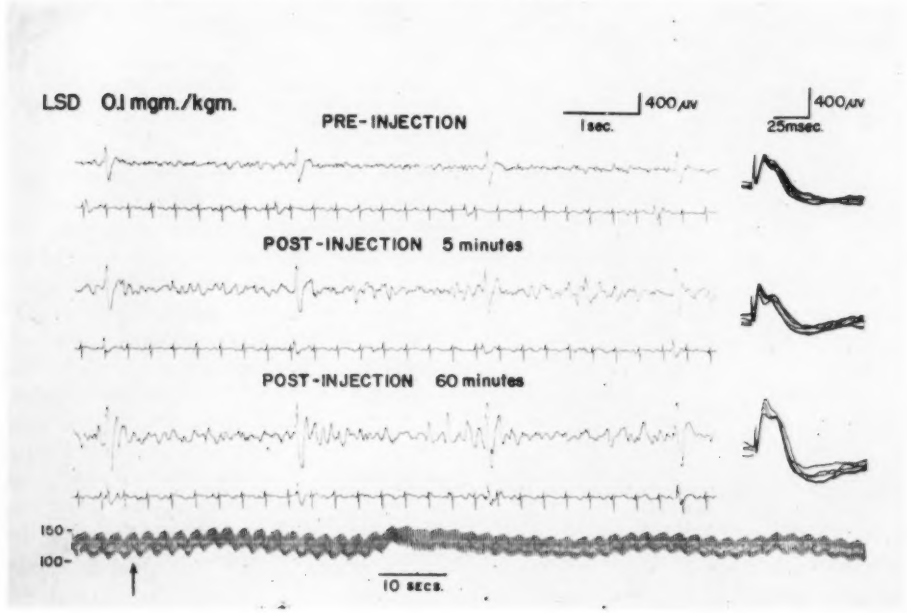


Fig. 4 (Cat 59).—Anectinized.
A, direct cortical response. LSD 0.25 mg/kg.
The lower channel of each EEG pair is the EKG.
B, blood pressure record. Arrow: injection of LSD 0.25 mg/kg. Description in text.

Fig. 5 (Cat 71).—Anectinized.
A, direct cortical response. LSD 0.1 mg/kg.
The lower channel of each EEG pair is the EKG. Note the second negative peak in the CRO traces.
B, blood pressure record. Arrow: injection LSD 0.1 mg/kg.



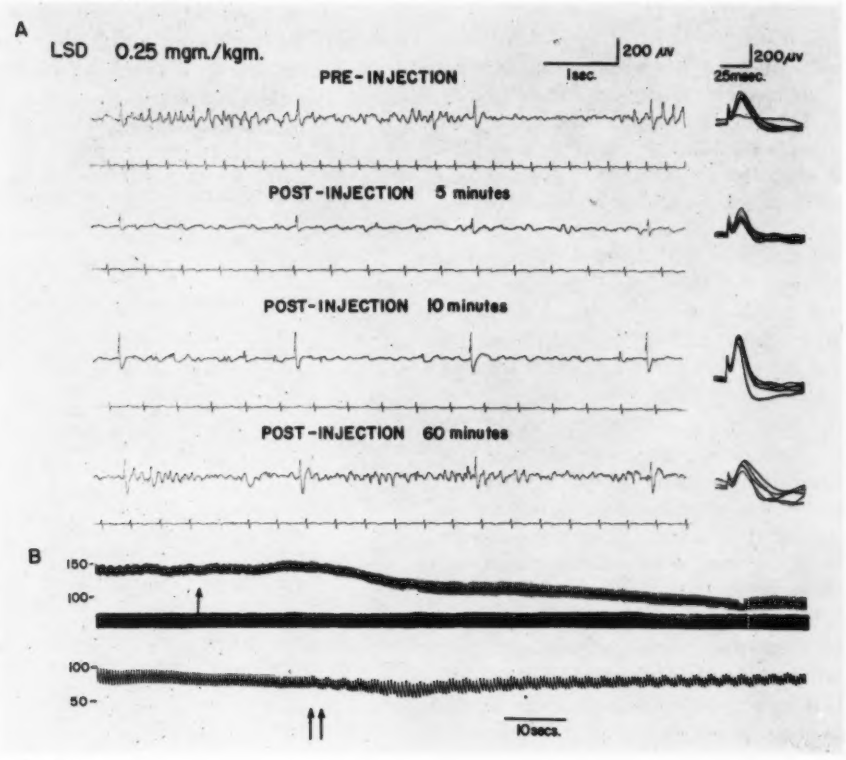
been a progressive increase in a positive wave following the primary negative deflection. It appears unlikely that LSD was responsible for a gradual increase over such a long time, since this was observed in only two animals. A possible explanation is a gradual change in the pressure of contact of the electrode with the cortical surface. On occasion, marked changes in the size of the shock artifact occurred in association with abolition of cortical activity and marked cardiovascular depression after large doses of LSD. This may have resulted in decreased volume of the brain and decreased contact of the electrode, which increased the resistance. In contrast, since it has been shown that the positive wave in Figure 5 has a higher response threshold

TABLE 4.—*Effect of LSD on the Direct Response of the Suprasylvian Gyrus* *
Pentobarbital

Animal No.	LSD, Mg/Kg.	Postinjection Times, Min. 2	5	10	20	30	60
70 †	0.1	115	130	80		80	65
70 ‡	0.1	75	95	85	75		55
68	0.25	95	50	145			90
69	0.25	70	30	30	45	55	60
69 †	0.25	45	0			0	
53	0.5	95	80	80	90	85	85
65	0.5	130	70	0		0	
66	0.5	110	135	140		120	105
67	0.5	80	0	50	95	95	90
66 †	0.5	145	150	115		115	90
68 †	0.5	100	0			0	
54	0.75	125	125	120	120		115
67 †	1.0	90	115		130		105
54 ‡	4.0	100	105	115	115	115	

* Postinjection mean amplitudes are expressed in percentages of preinjection mean amplitudes.
† Second injection.
‡ Third injection.

Fig. 6 (Cat 68).—Pentobarbital.
A, direct cortical response. LSD 0.25 mg/kg.
The lower channel of each EEG pair is the EKG. Description in text.
B, blood pressure record. Arrow: injection of LSD 0.25 mg/kg. Note cessation of respirations after injection.



than the preceding negative wave,[5] the increase of the former in this experiment may be explained on the basis of more effective contact between the electrode and the cortex.

Table 4 lists the data for the effects of LSD on the direct response in animals anesthetized with pentobarbital. Complete abolition of evoked potentials and 50% increase are seen in different preparations. In Figure 6 there is a 50% decrease, followed by an equally marked increase and then recovery, after 0.5 mg/kg. of LSD. In this animal severe respiratory depression occurred within a few seconds following injection, as shown in Figure 6*B*. Artificial ventilation was not used, and the animal remained apneic for four minutes. At this time respirations began again spontaneously; the blood pressure increased, and the evoked potentials regained control amplitude. The evoked potentials then increased to 145% of the control and one hour after injection had returned to normal.

Effects on Peak Time of Initial Negative Wave.—Changes in evoked potentials other than an increase or decrease in amplitude, e. g., changes in configuration, latency, or duration, may occur as manifestations of a drug effect. It has been noted that a second negative peak was seen occasionally in the direct cortical response (Fig. 5). In one animal injection of LSD was followed by obliteration of the second negative wave without a change in amplitude of the initial negative wave. Ten minutes following injection it had reappeared but did not regain preinjection amplitude.

Attempts to measure the latency of the direct cortical response were unsuccessful because of difficulty in controlling the amplitude of the shock artifact. However, in a series of 10 injections measurements were made of the time between the beginning of the shock artifact and the peak of the negative wave, immediately before and several times after the administration of LSD. Initial negative peak times varied from 9.7 to 17.0 msec., but within a series of 10 consecutive sweeps the variation was usually less than 10%. Following LSD, changes in peak time were dependent on changes in amplitude, prolongation of conduction time occurring with a decrease in mean amplitude of 50% or more. The maximum increase in peak time was 4.4 msec. and occurred when there was a 75% decrease in amplitude of the evoked potentials. Following two injections there was an increase in amplitude of the evoked potentials, associated with a decrease in peak time of 3.4 and 1 msec., respectively.

Cardiovascular Effects of LSD

The cardiovascular change most commonly observed after LSD was bradycardia. This occurred uniformly after all doses except 0.1 mg/kg. Furthermore, in most experiments the bradycardia outlasted whatever changes occurred in cortical activity. With large doses there was frequent cardiac arrhythmia, which at times progressed to brief periods of asystole. However, in none of the experiments did LSD cause death of the animal, despite profound cardiovascular and respiratory effects. Marked variation was seen in blood pressure re-

TABLE 5.—*Mean Arterial Blood Pressure in All Animals with Inhibition of Evoked Potentials of 50% or More*

Animal No.	LSD, Mg/Kg.	Control	Postinjection Times, Min. 2	5	10	20	60
		Succinylcholine					
57	0.5	125	35				170
57 *	0.5	135	85	100			
50	1.0	160	50		50		
54	1.0	135	0	55	20		
55	2.0	130		30	50		
73 †	3.0	145	85	165	165		165
77 †	3.0	100	55	110			
		Pentobarbital					
68	0.25	150	80	100	130		
69	0.25	165	80	105	110	110	140
69 *	0.25	115	85	145	160		
65	0.5	140	20	60	70		
67	0.5	150	40	80	90	100	
75 ‡	1.0	130	60	95		130	120
79	2.0	120	45	60	60	120	

* Second injection.
† Third injection.
‡ Fourth injection.

TABLE 6.—*Incidence of Severe Respiratory Depression Following LSD*

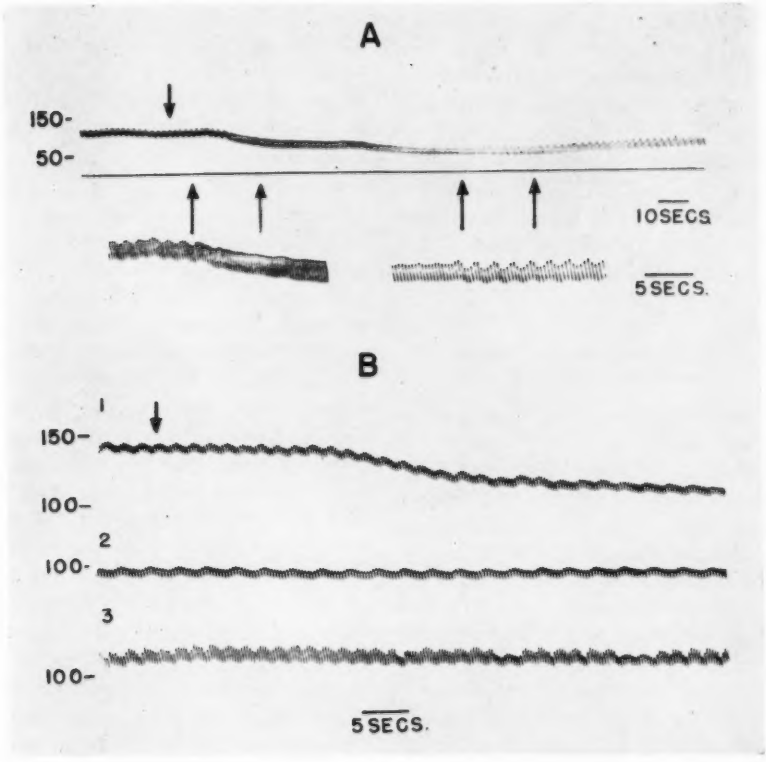
LSD, Mg/Kg.	No. of Injections	Respiratory Depression	Respirator	Recovery
0.05	6	0	--	--
0.01	4	2	1	2
0.25	9	4	3	4
0.5	6	3	3	3
1.0	3	2	2	2
2.0	1	1	1	1
3.0	1	1	1	1

sponses. As shown in Figure 6*B*, the blood pressure was reduced to shock levels by 0.25 mg/kg., but in other experiments 1.0 mg/kg. produced only transient hypotension.

An attempt was made to correlate blood pressure changes with alteration in cortical activity following LSD. Table 5 lists the mean arterial blood pressures of all animals in which there was at least a 50% decrease of evoked potentials after injection of LSD. In each instance there was a significant fall in blood pressure, and after 9 of 14 injections the pressure was decreased to 60 mm. Hg or less. However, after five injections the blood pressure was reduced to 60 mm. Hg, but the evoked potentials were not markedly inhibited.

Fig. 7.—*A* (Cat 84), pentobarbital. The top trace is the blood pressure record. Note the cessation of respiratory excursions after LSD 0.5 mg/kg. At the point midway between the arrows on the right the respirator was turned on. Prior to this, slight spontaneous respiratory excursions have begun. Lower traces: enlarged (×3) segments of top tracing (indicated by arrows) to show more clearly the respiratory pattern.

B, (Cat 85), pentobarbital. *1*, injection of LSD 0.05 mg/kg., indicated by arrow; *2*, 2 minutes after injection; *3*, 10 minutes after injection. Note the decrease in respiratory rate at *2* minutes and return to normal at 10 minutes.



The Respiratory Effects of LSD

Table 6 lists the incidence of severe respiratory depression following various doses of LSD.

Respiratory changes following approximately half of the injections without a significant relationship of dose to effect except that they were not observed in any animal given 0.05 mg/kg. In Figure 7*A* cessation of respiratory movements followed 0.5 mg/kg. of LSD. The lower inserts are enlarged segments of the same record to demonstrate more clearly the changes which occurred immediately after the drug was given and at the time artificial ventilation was begun. It is evident that prior to starting the respirator slight spontaneous breathing had returned. After two injections (Table 6) apparent apnea occurred and artificial respiration was not used. In both instances natural respirations returned within five minutes. The results for one of these animals are illustrated in Figure 6. Table 6 also shows that there were no deaths from respiratory depression irrespective of whether or not the animals were artificially ventilated.

Figure 7*B* illustrates the observation that changes in respiratory rate frequently followed small doses of LSD. In this animal the rate has been reduced by one-half following the administration of 0.05 mg/kg. of LSD.

Effects of Succinylcholine and Tubocurarine on Cortical Activity

It is undesirable to give additional pharmacological agents to animals which are used to evaluate the effect of a given drug, but in the majority of experimental designs this is unavoidable. In these experiments every animal received either pentobarbital or ether and succinylcholine. The influence of pentobarbital on the action of LSD was included in the study, and it was assumed that the effect of ether could be disregarded two hours after cessation of anesthesia.

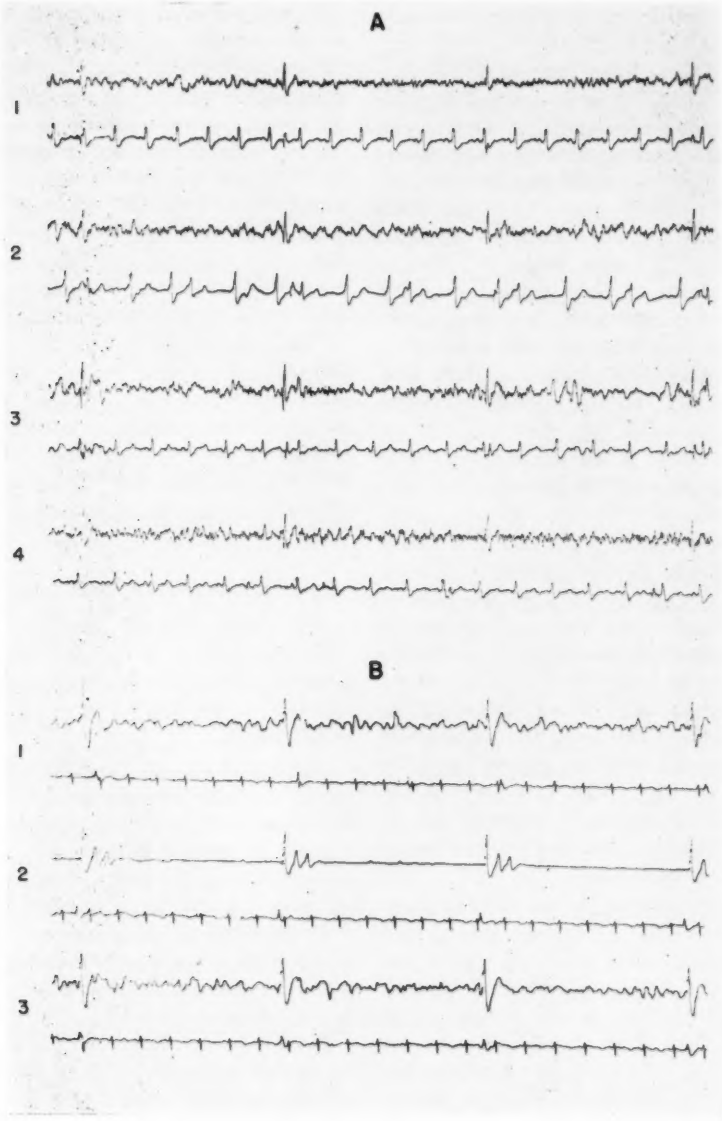
In a majority of the animals EEG records were obtained during the injection of succinylcholine. After injection of 20 mg., the dose used for immobilization of the animal, some effect on either cortical activity or the EKG was noted in about one-fourth of the animals. These effects were always transient, rarely lasting more than two minutes. In rare cases profound changes in both the EKG and cortical activity were observed, as illustrated in Figure 8*A*. In this animal, after the intravenous injection of 20 mg. of succinylcholine chloride, marked cardiac arrhythmia occurred within 20 seconds without a significant change in cortical activity. Forty-five seconds after injection the amplitude of the transcallosal potential was two times the control amplitude and the cardiac rhythm had returned to normal. Ninety seconds after injection both records show normal activity.

A variety of effects occurred in other animals, but the most commonly observed change was cardiac arrhythmia. When profound EKG changes were observed, there were parallel changes in the blood pressure. Usually this consisted of a very rapid fall in pressure, which was never great, followed by a rise to control level within a few minutes.

In a few animals, 3.0 mg/kg. of tubocurarine U. S. P. was given intravenously in order to compare its effects on the cortex with those of succinylcholine. Direct cortical potentials were investigated, and the response illustrated in Figure 8*B* was observed after most of the injections. There was abolition of the electrocorticogram two minutes after injection, but no change in the amplitude of the direct response was observed at any time. Recovery of spontaneous cortical activity was slow, but one hour following injection of the drug it had returned to normal. The waves following each evoked potential (*B2*) were also observed occasionally during marked cortical depression following LSD. These may be analogous to the rhythmic after-discharges observed by Chang [4] in sensory cortex. He found that these were more clearly discerned in animals with cortical depression

from pentobarbital (Nembutal). However in another publication [6] he noted that after-discharges were not seen in association with the transcallosal evoked potential, which is more closely related to the direct response than are cortical sensory potentials.

Fig. 8 (Cat 77).—*A*, Anectinized cat. Succinylcholine chloride 20 mg.
Transcallosal evoked potentials. *1*, preinjection; *2*, postinjection, 20 seconds. Note the marked cardiac arrhythmia. *3*, postinjection, 45 seconds. Note the increase of the transcallosal evoked potentials. *4*, postinjection, 90 seconds. Further description in text.
B, (Cat 77).—Anectinized cat; tubocurarine U. S. P. 3.0 mg/kg.
Direct cortical response. *1*, preinjection; *2*, postinjection, two minutes. Note the waves, suggesting after-discharge. *3*, one hour after injection.



Comment

The effect of LSD on the transcallosal evoked potential and the direct cortical response were no more consistent than the effects of LSD on sensory cortex.[15] Occasionally 0.25 mg/kg. produced complete abolition of cortical activity, whereas in another animal 4.0 mg/kg. produced no detectable effect. In general, profound depression of all cortical activity occurred more frequently than in the previous study.

These results differ from those of Marrazzi and Hart,[16,17] who reported decrease of the negative component of the transcallosal evoked potential following intracarotid doses of LSD as small as 0.008 mg/kg., and of Purpura,[21] who found that 0.025 mg/kg., injected intravenously, decreased the suprasylvian-striate response, which is also considered to be a cortical dendritic potential. Marrazzi and Hart used pentobarbital-treated (Nembutalized) animals exclusively, whereas Purpura's animals were unanesthetized. In the present investigation, differences in the effect of LSD on evoked potentials in anesthetized and Anectinized animals were considered too variable to be significant.

The cardiovascular and respiratory effects observed are in general agreement with the findings of Cerletti.[3] In cats anesthetized with chloralose and urethan, hypotension and respiratory depression were seen after 0.04 mg/kg. of LSD. Bradycardia was also seen uniformly, and Cerletti states that, in his experience, tachycardia has not occurred in any pharmacological preparation after LSD. With rather small intracarotid doses, Ingvar and Söderberg[13] reported an increase in blood pressure and increased cerebral vascular resistance.

In several animals in the current study marked depression of cortical activity and blood pressure followed 1.0 mg/kg. or less of LSD, but subsequent injections of 1.0, 2.0, or 3.0 mg/kg. produced only slight changes. Although the number of examples is small, these results suggest that tolerance to the drug has developed. In these experiments multiple injections were given no less than one hour apart. There have been few comments on the development of tolerance to LSD in acute animal preparations, but several investigators have shown that daily doses of approximately 0.001 mg/kg. administered to human subjects resulted in tolerance to the psychotomimetic effects of LSD after seven days.[1,7,14]

In two series of experiments[15] we have failed to find a significant effect of LSD on several different cortical evoked potentials, and changes in the natural activity of the cortex occurred only with large doses. On the basis of these experiments it might be concluded that the cortex is relatively insensitive to LSD, and, therefore, it is unlikely that the psychotomimetic effects in man are caused by an action of LSD on the cortex. However, there is a paucity of information on the neurophysiological signs of both drug-induced and functional disturbances of the mind.[12] Therefore, it seems more likely that these results reflect the inadequacy of present electrophysiological techniques in evaluating drugs that affect behavior, and that they do not necessarily eliminate the cortex as a site of action of LSD.

Summary and Conclusions

The effects of LSD on the transcallosal evoked potential and the direct cortical response were investigated in 26 cats. Doses from 0.1 to 4.0 mg/kg. were administered intravenously.

There was a marked inconsistency in the effects of LSD on the evoked potentials. Occasionally, 0.25 mg/kg. produced inhibition of all cortical activity, but in several animals 3.0 mg/kg. had no detectable effect on the amplitude of the evoked potentials.

Prolongation of conduction time occurred in association with a marked decrease of the initial surface-negative wave of the direct cortical response.

In a majority of the animals a decrease of evoked potentials of 50% or more occurred only in association with bradycardia,

arrhythmia, marked hypotension, and, in the anesthetized animals, respiratory depression.

The effects of succinylcholine and tubocurarine on cortical activity were investigated in several animals.

We wish to acknowledge the valuable criticism of Dr. A. Earl Walker in the evaluation of these experiments.

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Lateralization of Cerebral Lesion and Performance on Spatial-Temporal Tasks

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Research concerned with the relationships between the hemispheric locus of a cerebral hemisphere lesion and observable changes in psychological performance has been fairly consistent in finding a decrement in verbal ability associated with lesions in the dominant (left in right-handed patients) hemisphere.[1,5,7,9,12,13,15] Although such findings are often helpful in clarifying the nature and extent of verbal impairment, they hardly represent a remarkable discovery for the neurologist, who has long been aware of the high correlation between damage to the dominant hemisphere and dysphasia.

Studies which have dealt with brain damage and its relationships to spatial or spatial-temporal tasks (where such tasks are distinguished by the perception of elements of a spatial configuration either simultaneously or successively over time) have not provided as clear a picture. Clinical studies of patients with lesions restricted to the right hemisphere have demonstrated that such lesions may be associated with spatial or spatial-temporal impairment.[3,4,8,10,11] However, since such studies have been concerned with selected cases, they are expository rather than statistical in character, and thus provide no evidence as to the relative frequency of such impairment in a larger sample of right hemisphere cases.

A second line of research dealing with spatial (or spatial-temporal) performance and brain damage has directly compared patients with lesions localized in the left hemisphere with patients judged to have right-sided lesions. McFie and Piercy[7] found a left hemisphere group to be inferior on two verbal tasks (verbal retention and similarities), while right-sided patients performed more poorly on spatial tests (visual retention, Block Design, and Picture Arrangement). Andersen,[1] utilizing Wechsler-Bellevue Intelligence Scale[14] subtests, found consistent differences on verbal tasks between dominant and nondominant hemisphere groups in the direction of greater impairment on the part of patients with dominant hemisphere lesions. However, he was able to secure evidence for differential performance (nondominant group poorer) on only one of the five performance measures, most of which were spatial in character. Reitan[12] also compared left and right hemisphere groups on the Wechsler-Bellevue Scale and found that the left-sided group was significantly inferior on five of the six verbal scale tests. However, though the scores of the group with right hemisphere pathology were consistently lower than those of the left-sided group on the five performance measures, none of the differences was significant. Using measures obtained before and after temporal lobectomy in right-handed patients, Meyer and Jones[9] found a significant decline in scores for the *dominant* hemisphere group upon *both* verbal (Wechsler-Bellevue Verbal Scale, Mill-Hill Vocabulary Test) and spatial (Wechsler-Bellevue Performance Scale, Raven's Matrices) tasks. However, pre- and postoperative measures for the *nondominant* cases showed no change following surgical intervention on either verbal or spatial tasks. Heilbrun,[5] using verbal and spatial

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test batteries, was able to demonstrate an over-all difference on the verbal battery between left and right hemisphere cases only when patients with clinically evident dysphasia were included in the left-sided group. There was no over-all difference on the spatial battery between the groups, whether the dysphasics were considered or not, but in the latter case two of the seven tests in the spatial battery (Block Design and Picture Arrangement) were associated with inferior performance for the right-sided group.

Thus, studies of the association between performance on spatial tasks and hemispheric localization of cerebral lesion suggest a trend in the direction of greater impairment following right hemisphere damage (in right-handed patients). However, the evidence for this proposition is far from clear-cut. The failure to obtain unequivocal evidence may well be a function of undue confounding of verbal ability with spatial-task performance when attempts are made to measure the latter variable. Spatial tasks typically include verbal instructions by the tester, implicit verbal mediation of the motor responses, and, in some cases, an overt verbal response, which is scored. Consequently, it is difficult to determine whether poor performance on a spatial task by a patient with a left hemisphere lesion is due to a verbal impairment or to a distinctive inability to deal with spatial relationships. For example, Meyer and Jones[9] found that their patients with dominant-hemisphere lesions scored lower on the Wechsler-Bellevue Performance Scale than did those with non-dominant-hemisphere lesions, although the observed difference of 8 IQ points was not statistically significant. At first glance, this would appear to contradict the hypothesized relationship between right hemisphere damage and spatial deficit. However, the mean Verbal Scale IQ of patients with dominant-hemisphere lesions was 20 points lower than that of the non-dominant-hemisphere cases. Thus the possibility must be considered that this marked difference in verbal skills contributed to the reversal in the hypothesized relative performance of these groups on the measures of spatial ability.

It follows that careful control of a patient's verbal ability should be imposed when one attempts to clarify the neurologic basis for deficit in spatial abilities. Such a control was instituted in the present study, which compared performances of patients with hemispherically localized lesions upon various spatial tasks.

Procedure

The two brain-damaged groups utilized in this study were composed of patients with confirmed cerebral pathology. These were (1) a group with lesions judged to include the right cerebral hemisphere (RS) but not necessarily confined to it (i. e., right-sided and bilateral cases), and (2) a group with lesions judged to be fairly well confined to the left hemisphere (LS). No patient with clinically evident dysphasia was included in either group. The physically ill (control) group (C) was obtained from various medical wards and included only patients for whom there was no history or current suspicion of brain pathology. The groups were matched for age and Wechsler-Bellevue Verbal Scale IQ. The matching data are provided in Table 1.

All patients were right-handed, were capable of sustained testing, and had no history of psychosis or hospitalization for a mental disorder. The groups were obtained from the University Hospital or Veterans Administration Hospital, Iowa City. Performances of these patients were included in a previous paper by Heilbrun[6] but have been reanalyzed in the present study in such a way as to test directly the hypotheses under investigation.

The four spatial tasks included in this study were administered as part of a larger battery of tests and always appeared in the same order relative to the remainder of the battery. These tests were selected because they represent widely vary-

TABLE 1.—*Age and Verbal Intelligence Data for the Right-Sided (RS), and Left-Sided (LS), and Control (C) Groups*

	RS	LS	C
No.	31	15	15
Age			
Mean	45.9	45.9	44.5
S. D.	11.0	12.3	12.8
Verbal IQ			
Mean	93.7	91.2	93.1
S. D.	14.7	15.8	9.4

ing types of spatial performances and do not require any overt verbal response from the patient. The four tests are as follows:

1. Picture Arrangement: This test is one of the Wechsler-Bellevue Intelligence Scale performance subtests which required the patient to arrange several sets of pictures in such a way as to make a meaningful story. Among other determinants, performance on this task involves the temporal ordering of life events and the spatial positioning of the picture cards.
2. Block Design: This task required the construction of design patterns from a set number of individual blocks and is also a Wechsler-Bellevue performance subtest.
3. Serial Synthesis: Meaningless geometric designs were broken up and parts presented consecutively. Following an immediate memory procedure, patients were presented with a multiple choice of designs and asked to select the one representing the parts combined into a single unit.
4. Visual Retention Test (Form C)[2]: This is an immediate memory test which involved graphic reproduction of meaningful geometric designs.

All patients were also administered the six verbal subtests of the Wechsler-Bellevue. The verbal IQ score based on these subtests was used as the measure of verbal ability in this study.

Results

The spatial test data in this investigation were analyzed in two fashions to evaluate the hypothesis of differential spatial loss associated with right hemisphere lesions when compared with the effects of left hemisphere pathology.

Analysis I involved the comparisons of both the right and the left hemisphere group with the physically ill (control) group, with all groups matched for verbal intelligence. These comparisons, given in Table 2, demonstrate quite clearly that patients with right-sided pathology were consistently inferior on spatial tasks relative to a non-brain-damaged control group. It is equally clear from these data that there were no differences in performance level on these tasks between patients with left hemisphere involvement and the same control patients.

Analysis II represented a direct and more precise comparison of right and left hemisphere groups only. In this analysis a larger pool, of 71 patients, with confirmed cerebral pathology (which included the 45 patients in Groups RS and LS) was used to derive expected scores for the four tasks based upon level of verbal intelligence. These 71 patients were grouped into three classes: (1) verbal IQ, 90 or less (below average); (2) verbal IQ between 91 and 110 (average), and (3) verbal IQ 111 or above (above average). The mean score on each of the spatial tasks was determined for patients within each of the three IQ categories. These means (expected scores) were used as cutting points, and it was then possible to determine the number of RS and LS patients whose scores fell above and below expectancy. Each patient was compared, therefore, only with other brain-damaged patients within his own verbal IQ range. These comparisons are found in Table 3. It can be seen that when LS and RS groups are directly compared on spatial measures

TABLE 2.—*Comparison of Groups with Right Hemisphere Pathology (RS), Left Hemisphere Pathology (LS), and a Control Group (C) on Four Spatial Tasks*

	RS Mean	C Mean	LS Mean	*d. f.*	*t*	*P*
Picture Arrangement	5.45	7.27	..	..	..	0.10 *
Block Design	9.84	19.40	..	44	4.23	0.001
Serial Synthesis	4.16	5.47	..	44	1.96	0.05
VRT (C)	3.33	5.07	..	..	..	0.01 *
Picture Arrangement		7.27	8.07	28	0.45	0.70
Block Design		19.40	17.07	28	0.94	0.40
Serial Synthesis		5.47	5.60	28	0.14	0.90
VRT (C)		5.07	5.46	26	0.56	0.60

* The Cochran-Cox approximation was used because of heterogeneity of variance.

TABLE 3.—*Relative Frequencies of Right-Sided (RS) and Left-Sided (LS) Cases Which Fell Above and Below Expected Scores on Four Spatial Tasks*

	RS		LS			
	Below	Above	Below	Above	χ^2*	*P*
Picture Arrangement	22	9	5	10	4.46	0.05
Block Design	20	11	4	11	4.39	0.05
Serial Synthesis	22	9	5	10	4.46	0.05
VRT (C)	18	10	3	10	4.50	0.05

* All χ^2-tests are for 1 *d. f.*

with precautions taken to minimize the influence of differences in verbal ability, the differential impairment associated with right cerebral hemisphere pathology seems clear.

Comment

It was hypothesized that attempts to relate differential spatial impairment to right cerebral hemisphere pathology in right-handed patients have failed to produce consistent results because the tests of "spatial ability" may make greater demands on verbal skills than is usually assumed. Since verbal impairment is characteristically associated with left hemisphere pathology, the effect of such demands could be the masking of a relationship between spatial impairment and right hemisphere damage. The results of this investigation provide confirmation of the importance of verbal skills as a confounding factor in performance on many "spatial" tasks and, at the same time, support the hypothesis of an association between right hemisphere pathology and spatial deficit. When verbal intelligence level was controlled by group matching, it was found that right hemisphere cases were reliably inferior on spatial tasks than were physically ill, non-brain-damaged controls. In contrast, comparison of left hemisphere cases with the same control group showed no difference in performance level on these spatial measures. A direct comparison between left and right hemisphere patients, in which verbal differences were minimized both by group matching and by comparing a patient's performance with only those brain-damaged patients in his own verbal IQ range, demonstrated a consistently poorer spatial performance for the right hemisphere group.

These results provide evidence for the association of spatial disability with lesions within the right cerebral hemisphere of a right-handed person. No attempt was made to determine whether the disability could be more precisely related to a specific area within the right hemisphere because of the restricted size of the sample and because neurologic judgment regarding the site of lesion within a hemisphere often included two or more contiguous areas (e. g., fronto-parietal). These two factors made it impossible to make any stable inferences from the present data regarding more specific localization.

An implication of this study is that the investigator or the clinician who is interested in determining the site of focal lesions within the cerebral hemispheres associated with various types of behavioral impairment should be cognizant of the importance of verbal-symbolic impairment as a possible confounding factor. A dysphasic patient with a lesion restricted to the left hemisphere may perform poorly on all tests, including spatial tasks. Yet the present study supports the notion that defective performance on spatial tasks is differentially related to pathology of the right hemisphere. It would seem, therefore, that the effect of level of verbal skills should be held constant in evaluating level of performance on spatial tasks and making inferences about hemispheric locus of lesion from such evaluation. This should decrease the likelihood of localization error in clinical appraisal and help to clarify psychoneurologic relation-

ships in investigative work. One solution to this problem would be to construct norms, based on a substantial number of brain-damaged cases, which would allow the clinician to predict what level of performance on a given diagnostic task is expected for a given verbal IQ score. A score falling above expectancy would lead to one diagnostic judgment; a score below expectancy, another. A similar normative approach was suggested by Heilbrun [6] with reference to the application of the digit span test in the neurologic examination.

The finding that patients with left-hemisphere damage performed as well on spatial measures as did non-brain-damaged controls when matched for verbal intelligence, when taken in conjunction with the previous findings [5] that right-sided patients were not inferior to similar controls on verbal measures, would seem to clarify why attempts to discriminate between brain-damaged and appropriate non-brain-damaged groups with psychological measures usually meet with rather limited success (typically the proportion of correct classification is 65%-75%). If a verbal measure is used, right hemisphere cases may not be detected; if a "nonverbal" (e. g., spatial) measure is used, nondysphasic left-sided cases may be overlooked.

Summary

This study evaluated the hypothesis that a relationship exists between impaired performance on spatial or spatial-temporal tasks and right cerebral hemisphere pathology in right-handed patients. It was further hypothesized that undue demands upon verbal skills in tests used to measure spatial deficit have tended to mask the association between right hemisphere lesions and spatial impairment, since verbal deficit is typically associated with left hemisphere pathology. After elimination of patients with clinically evident dyphasia, comparisons were made on four measures of a group of patients judged to have cerebral damage involving the right hemisphere, a group judged to have damage primarily restricted to the left hemisphere, and a non-brain-damaged, physically ill, control group. These groups were matched for age and verbal intelligence. The results supported the hypothesis of a relationship between right cerebral hemisphere lesions and differential impairment in spatial skills in right-handed patients, as well as indicating the importance of verbal ability as a confounding factor. Implications of these results for neurologic research and clinical neurology are suggested.

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Subcortical Recording in Temporal Lobe Epilepsy

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Introduction

It is now generally assumed that psychomotor epilepsy is of temporal lobe origin, although psychomotor phenomena may occur in association with discharges arising in areas quite remote from the temporal lobe. In fact, because the phenomenology of psychomotor epilepsy includes practically all of the possible cerebral functions—somatic, visceral, and psychic—one would doubt, a priori, the constant origin of such discharges from one source. It therefore becomes particularly pertinent, in patients being considered for temporal lobectomy, to demonstrate that psychomotor phenomena are of temporal origin before an excision of the lobe is advised.

The series reported here consisted of 14 patients, having medicinally uncontrollable psychomotor epilepsy, who were referred for consideration of surgical intervention. Because the seizures or electroencephalographic findings were atypical, it was considered advisable to study in some detail the activity of the brain in areas somewhat removed from the temporal lobe by means of depth electrodes.

Technique and Depth Recording

Only after complete physical, neurological, and electroencephalographic studies of the patient had disclosed no contraindication to surgical intervention were depth electrodes inserted into the brain. Under aseptic conditions, and after local infiltration of the scalp with 1% procaine hydrochloride, small twist-drill perforations were made in the frontal and parietal regions and a burr hole made in the temporal region. Six electrodes of No. 38-gauge double Formvar nicochrome (Nichrome), wire,* bared at the tip for approximately 1 mm., were passed into a No. 20-gauge needle, approximately 9 cm. in length. The tips of the six strands of wire were staggered at 1 cm. intervals. This needle was then inserted through the cranial perforations to the desired positions within the brain. The tress of electrodes was held as the needle was slipped out over the fine wires, which remained in place. Each tress was fastened with one silk suture through the scalp. A fractional pneumoencephalogram was made immediately, and the location of the tips of each strand of wire calculated by reference to the position of the cerebral ventricles and the bony landmarks of the skull. Several stereotactic atlases and cross sections of the brain were used to locate as accurately as possible the position of the tips of the various electrodes. Usually the wires were left in place for 10 to 30 days, recordings being made at intervals of 1 to 3 days. Prior to removal of the tresses, roentgenograms of the skull were made to confirm their final position. After removal, the length of the tresses within the intracranial cavity were remeasured, and the wires were checked for faulty insulation.

Recording was carried out on an 8-channel Grass electroencephalograph or on a 16-channel Gilson electroencephalograph. Records were usually made both from the depth electrodes and from representative surface electrodes, particularly temporal derivatives, and on some occasions sphenoidal electrodes. During the recording, activation techniques, such as hyperventilation, sleep, pentylenetetrazol (Metrazol), and photic driving, were used, and electrical stimulation of the depth electrodes was carried out, using both sine-wave and square-wave pulses at voltages varying from 0.5 to 10, and at frequencies varying from 15 to 60 per second.

During the recording, both before and after stimulation, the patient was closely questioned regarding any subjective phenomena which might be associated with the stimulation. Careful observation was made of the patients at all times for psychic or motor phenomena.

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TABLE 1.—*Comparison of Depth and Scalp Spontaneous Discharges*

Case	Amount of Record Analyzed, Min.	Number of Spikes	
		Surface Leads	Depth Electrodes
1	12.5	47	53
2*	11	7	33
3	14.6	10	4

* In two of four instances, spikes apparently originating from the cortex (high voltage in scalp leads) were not seen in the depth electrodes.

Results

Before discussing the particular findings of this study, it may be well to consider the relationship of the scalp and depth recordings. In three patients samples of traces from depth and superficial electrodes were analyzed to determine the degree of correlation of the spikes.

The surface electrodes having the largest spikes were compared with the depth electrodes having the highest and most frequent discharges. To be considered spikes, the discharges had to have a rapid gradient voltage of 100μv. in one set of electrodes. A compact burst of spikes was considered as a single spike for this analysis.

It is apparent from Table 1 that the relationship of surface to depth spiking varies considerably. In some patients the surface electrode appears to pick up more spikes than the depth electrode, and in other cases the reverse is true. A brief glance at some of the records will indicate that the depth electrodes probably pick up activity only from an area of a cubic centimeter or so and that electrodes 1-2 cm. distant from a focus of several hundred microvolts will show no activity. It would seem probable that the activity on the surface is dependent upon at least two factors: one, the proximity to the surface of the cortex which is giving rise to the firing, and the second, propagation from deeper structures to cortex near the scalp electrodes. There is great variation in the consistency with which depth spiking is picked up not only by surface electrodes but also by sphenoidal leads. In Figures 1 and 2, it is seen that depth activity in the temporal lobe may be rather pronounced, although traces from sphenoidal electrodes have no abnormality correlating with that from the depth electrodes.

This observation is quite in line with many previous reports of depth recording and correlates well with Abraham and Marsan's [1] comparison of the activity recorded from surface and depth electrodes. They found that anterior temporal spike foci could not be seen on surface electrodes anteriorly in 6%-12% of cases and in posterior temporal electrodes in approximately 20% of cases.

Protocols of two patients studied in this series will be outlined to indicate typical findings.

CASE 1.—This 40-year-old white man was admitted because of frequent, uncontrollable lapses of consciousness. He had had a normal birth and no unusual childhood illnesses. At the age of 16 years he began to have nocturnal grand mal attacks, which he recognized as having occurred by a tired feeling the following morning. Two years later he was given phenobarbital, and the frequency of the attacks decreased. At about that time he became aware of brief lapses of consciousness during the day. The major attacks occurred usually at night and were controlled well by diphenylhydantoin (Dilantin) and phenobarbital. No grand mal seizure has occurred in the past year. However, he continued to have minor episodes, consisting of a sense of numbness of the left arm, such as preceded his occasional daytime major attacks. With this sensation he had a period of loss of contact with his environment for a few seconds to a minute. He was rather depressed and attempted suicide.

The general physical and neurological examinations were normal. The routine electroencephalograms showed high-voltage spiking in the anterior and posterior temporal regions, with some low-voltage theta and delta activity slowing over the whole right hemisphere. Succeeding records indicated that most of the abnormalities were confined to the right temporal region.

On Sept. 17, 1957, four sets of six-filament wire electrodes were inserted into the right temporal and frontal lobes (Fig. 3). Depth records were made on Sept. 19, 21, 22, 25 (two sets), 27, and 28. On Sept. 19 recordings were made from all depth electrodes. The basic activity consisted of a dominant frequency of 8-11/sec. with a few ir-

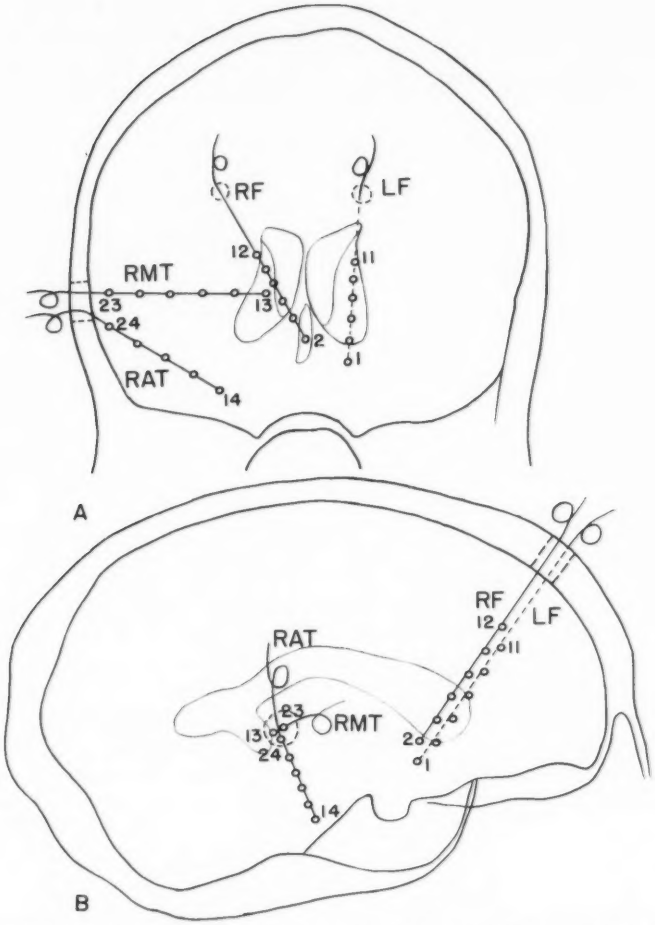


Fig. 1.—Diagram to indicate the site of the depth electrodes as determined from pneumoencephalograms. The calculated locations of each electrode are as follows:

RF tress: 2, septum pellucidum or lateral ventricle; 4, ventricle; 6, ventricle; 8, cingulate gyrus; 10, cingulate gyrus or white matter; 12, white matter.

LF tress: 1, head of caudate nucleus; 3, ventricle or corpus callosum; 5, ventricle or white matter; 7, frontal white matter; 9, frontal white matter; 11, frontal white matter.

RAT tress: 14, hippocampal gyrus; 16, fusiform cortex; 18, white matter; 20, middle temporal gyrus; 22, superior temporal gyrus; 24, surface.

RMT tress: 13, nucleus ventralis lateralis of thalamus; 15, internal capsule; 17, putamen; 19, insula or temporal operculum; 21, white matter, superior temporal gyrus; 23, superior temporal cortex.

regularities. At times, this pattern was interrupted by bursts of spiky discharges of moderate voltage in the anterior and middle temporal leads with rare independent small spikes posteriorly. At times, high-voltage slow-spike discharges, beginning in the right anterior temporal leads (9, 10, 11, 12) would spread within two seconds throughout the temporal leads, but with little disturbance in the right orbitofrontal cortex. In the posterior medial temporal structures (cingular gyrus) a spike-wave pattern predominated and persisted for several seconds after the spiky anterior temporal activity. These bursts were unassociated with overt clinical phenomena (Fig. 4).

On Sept. 21 scalp and depth recordings were made which exhibited the same basic pattern as that on Sept. 19. A number of spontaneous electrical seizures appeared having synchronous dis-

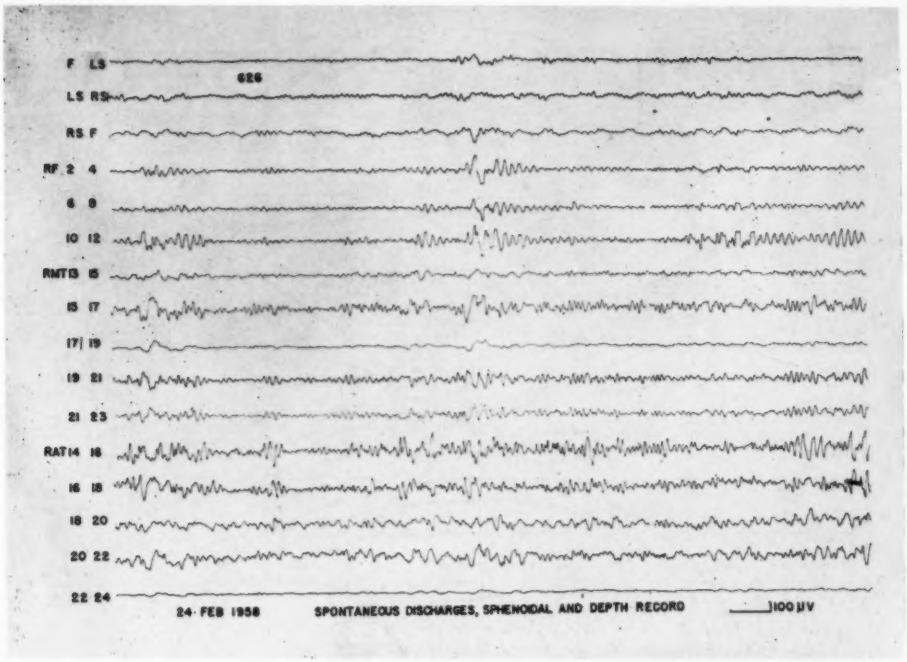


Fig. 2.—Electrograms from depth and sphenoidal electrodes to show the inconstant recording in the sphenoidal leads of the spontaneous spiky activity in the right medial temporal and cingulate leads (*F*-midline forehead, *LS*, left sphenoid, *RS*, right sphenoid). The patient, a 33-year-old man (same case as that in Figure 1), had seizures consisting of brief lapses of consciousness and automatisms, preceded by a sensation in the throat. In surface recordings a right temporal spike focus was present.

charges in the anterior, middle, and posterior temporal leads, being most marked in the hippocampal gyrus and piriform cortex. The disturbance consisted of 2/sec. waves of highest voltage in the occipital leads and in the depth electrodes of the cingulate gyrus.

Some 29 stimulations of the depth electrodes were made, obtaining after-discharge lasting 10-15 seconds, without clinical concomitants.

On Sept. 22 a record was made stimulating eight of the subcortical electrodes. Except for transient after-discharge, no electrographic or clinical phenomena were noted. In the morning of Sept. 25 a record was made with stimulation of 15 of the subcortical electrodes. From stimulation of the right amygdala (5 volts, 60/sec., five seconds), an after-discharge resulted locally, and the patient complained of a peculiar sensation in his left side.

In the afternoon of that day a second record was made. Pentylenetetrazol was given intravenously (200 mg.), producing within four minutes both an electrical and a clinical attack (Fig. 5). The patient commented, "One of those spells again." The highest-voltage spikes were seen in the uncinate and hippocampal leads. The wave form at any one point changed as the attack progressed, but the activity was poorly reflected in the surface recordings.

Approximately 20 minutes after the administration of pentylenetetrazol the record seemed to have regained its usual pattern. At that time stimulation of the right amygdala (5 volts, 60/sec., five seconds), induced prolonged local after-discharge, as well as spiking in the remainder of the right temporal lobe. The character of these discharges varied from lead to lead and from time to time. In the surface electrodes, the changes were less pronounced than in the depth electrodes. The discharges ended abruptly with a synchronous burst at all points. The seizure was associated with poorly characterized subjective sensations, described as something in the arms, spreading and getting worse (Fig. 6).

Stimulation of these amygdala electrodes was repeated many times, with similar effects and reproduction of the patient's feelings preceding his attacks.

On Sept. 27, 1957, another recording from the subcortical leads was made, and 109 stimulations

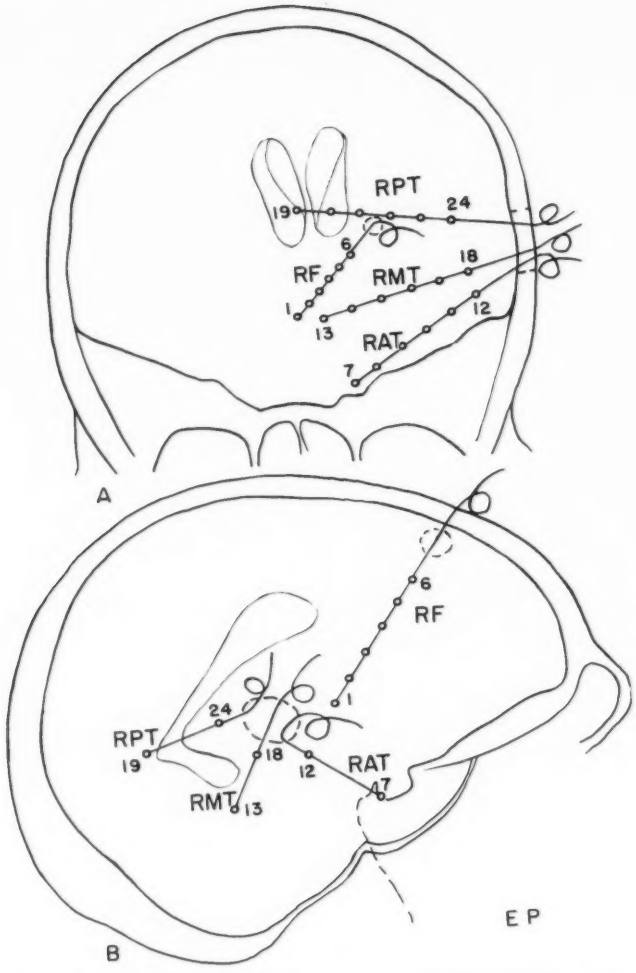


Fig. 3 (Case 1).—Diagram of the position of depth electrodes based upon roentgenographic localization in pneumoencephalograms. The calculated location of each electrode is as follows:

RF tress: 1, r. fornix; 2, corpus callosum; 3, cingulate gyrus; 4, white matter; 5, white matter; 6, white matter.

RAT tress: 7, r. pyriform cortex; 8, amygdala; 9, periamygdala; 10, superior temporal gyrus; 11, superior temporal gyrus; 12, superior temporal gyrus.

RMT tress: 13, r. hippocampal gyrus; 14, r. hippocampal gyrus; 15, r. hippocampal gyrus; 16, white matter; 17, white matter; 18, white matter.

RPT tress: 19, r. cingulate gyrus; 20, r. cingulate gyrus; 21, r. cingulate gyrus; 22, ventricle; 23, white matter; 24, white matter.

were made. Aside from local after-discharges, no responses were obtained.

On Sept. 28 a record was made from the subcortical electrodes, some eight stimulations being carried out.

The wires were removed on Sept. 28, 1957.

On Nov. 22, 1957, a right temporal craniotomy was performed. The cortex appeared normal. Electrodes were placed on the surface of the brain and inserted into the anterior and posterior temporal regions, as well as the amygdala. There was cortical and depth spiking. Stimulation of the

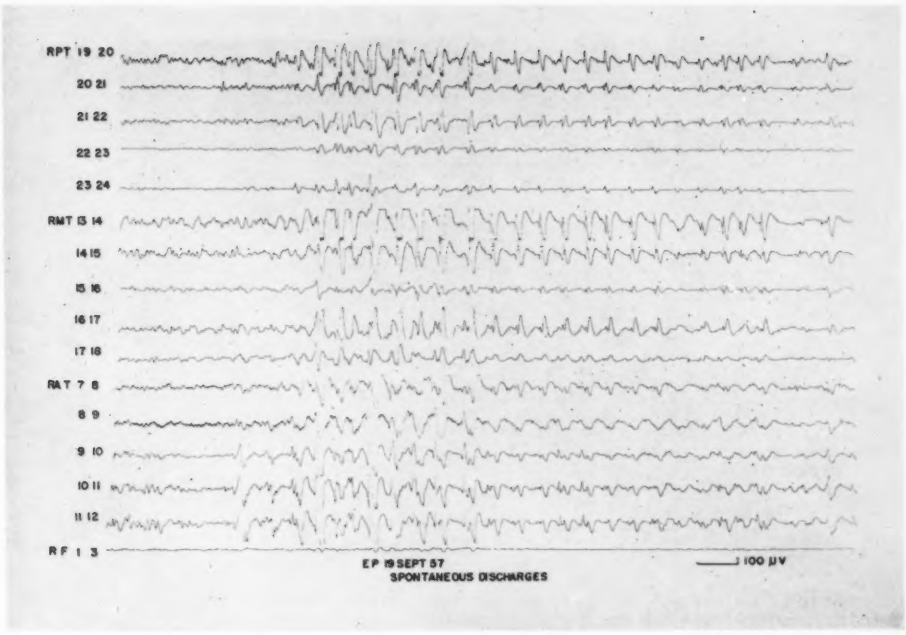
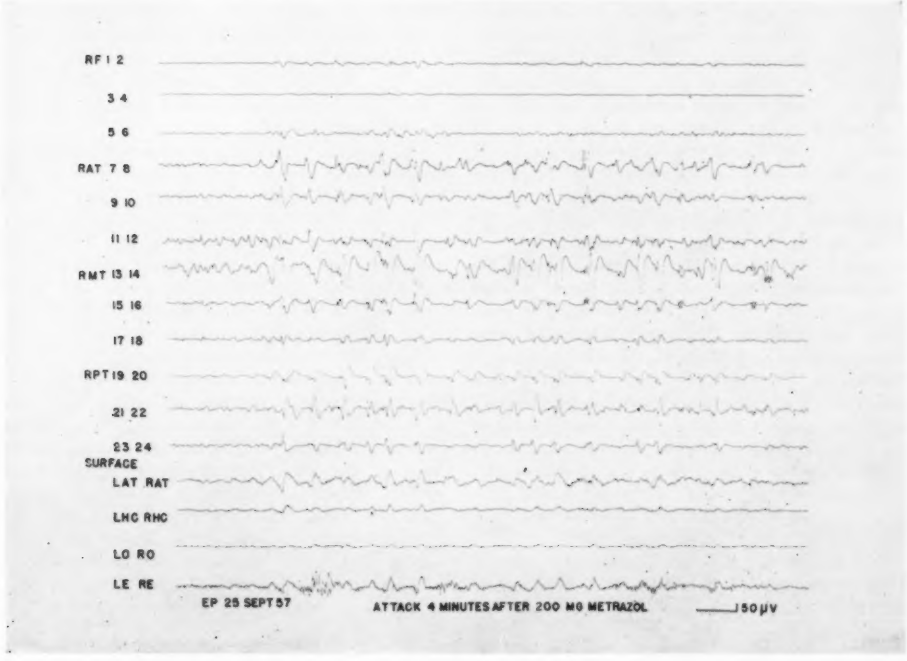


Fig. 4 (Case 1).—Spontaneous synchronous discharges throughout the temporal lobe, including the hippocampus (*RMT 13-14*) and amygdala (*RAT 7-8-9-10*) and the cingulum (*RPT 19-20-21*), while the patient was awake and unaware of their presence.

Fig. 5 (Case 1).—Four minutes after the intravenous administration of 200 mg. of pentylenetetrazol (Metrazol), high-voltage spiking appeared in the temporal region, particularly in the right pyriform-amygdala (*RAT 7-8*) and hippocampus (*RMT 13-14*) leads, and the patient noted "something happening, left side spreading—one of those spells again."



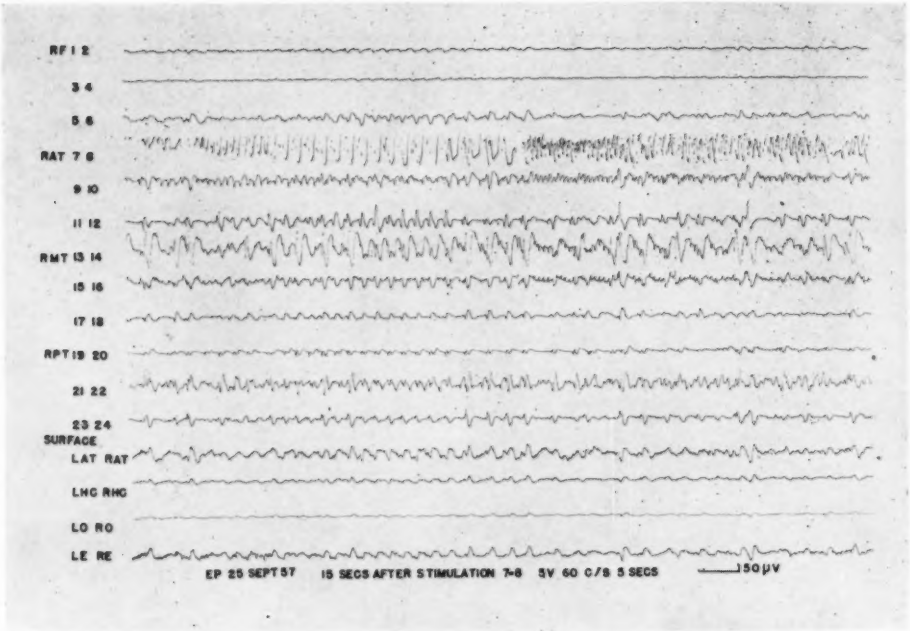


Fig. 6 (Case 1).—Stimulation of the right pyriform cortex-amygdala leads (*RAT 7-8*) produced widespread discharges, most marked in the hippocampus (*RMT 13-14*), though appearing prominently throughout the temporal lobe. During the after-discharge the patient felt "sensations" spreading in his arms, but did not lose consciousness.

middle depth leads (amygdala) elicited an aura like the spontaneous ones, together with after-discharges. Stimulation of the posterior depth leads produced an occasional aura. Incision was made into the second temporal convolution, and the second and third gyri were removed anterior to the vein of Labbé. Uncal stimulation then could still reproduce the aura; after removal of this structure, the aura could no longer be obtained by stimulation. On histological examination of the cortex and uncus a gliosis was noted.

Case 2.—A 16-year-old youth was admitted for the evaluation of frequent seizures from the age of 5 years. There was no history of natal or postnatal abnormalities. The spells originally were characterized by blinking of the eyelids, upward turning of the eyes, and then falling. Within recent years the patient had episodes in which he wandered about in a dazed state. During some of the spells he noted a sense of "sickness in his stomach." When without spells for several weeks, he seemed mentally clear; but when having frequent attacks, he had difficulty in expressing himself and poor powers of comprehension.

The general physical examination was normal. Mentally he seemed somewhat dull. The routine laboratory examinations, including examination of the spinal fluid and skull x-rays, were normal. The routine scalp electroencephalogram showed a grossly abnormal record of almost continuous seizure activity, consisting of generalized spiking and spike-dome activity, and isolated spikes in the left occipital region.

On July 17, 1956, six sets of six-filament electrodes were inserted into the frontal, temporal, and parietal regions of the brain (Fig. 7). Recording was carried out on six occasions. All depth recordings had bursts of spiky activity present in practically all leads at one time or another.

On July 23 electrical asymptomatic fits were noted in the frontal leads and electrodes in the right globus pallidus and internal capsule. Irregular spiking activity was present in the leads from the deep structures of the left temporal lobe.

On July 28 a spontaneous electrical seizure was recorded during sleep, beginning with synchronous bifrontal changes, and with high-voltage bursts later in the right globus pallidus and internal capsule. Spontaneous spiking in the right amygdala continued independently during the attack (Fig. 8).

Stimulation was carried out at all electrodes, producing after-discharges, and various hallucinations —abdominal cramps, "rotten" taste, epigastric sensations—were induced, but no episodes of confusion

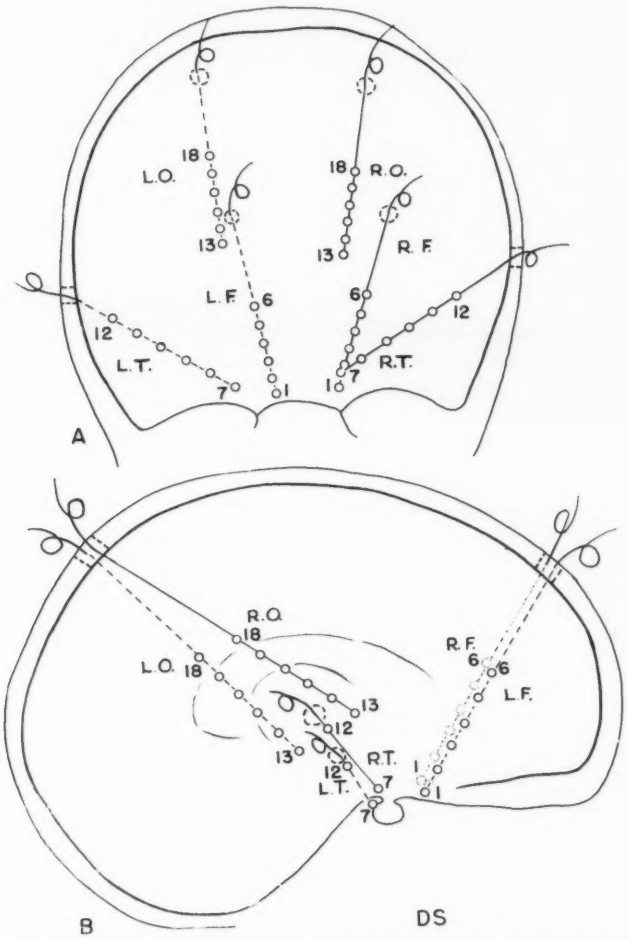


Fig. 7 (Case 2).—Diagram of depth electrodes made from roentgenograms of the skull. The calculated position of each electrode point is as follows:

RF tress: 1, r. orbital cortex; 2, white matter; 3, white matter; 4, white matter; 5, white matter; 6, white matter.

LF tress: 1, l. orbital cortex; 2, l. orbital cortex; 3, white matter; 4, white matter; 5, white matter; 6, white matter.

RT tress: 7, r. amygdala; 8, white matter; 9, insula; 10, insula; 11, insula; 12, superior surface, first temporal convolution.

LT tress: 7, l. amygdala; 8, amygdala or white matter; 9, insula; 10, insula; 11, insula; 12, temporal cortex.

RP tress: 13, r. globus pallidus; 14, r. globus pallidus; 15, r. globus pallidus; 16, internal capsule; 17, ventricle; 18, white matter.

LP tress: 13, l. hippocampal gyrus; 14, cornu ammonis; 15, lateral geniculate body or visual radiation; 16, ventricle or pulvinar; 17, ventricle or corpus callosum; 18, white matter.

or attacks resembling the spontaneous spells. Some of the after-discharges had widespread electrical effects.

On July 28, 1956, stimulation of the right amygdala induced a rapid spread of an after-discharge to the right frontal, temporal, and basal structures without clinical concomitants. The initial abnormality lasted 40 seconds, ending with bursts of asynchronous spikes in the right basal and frontal regions, with persisting high-voltage slowing in the same leads for over two minutes (Fig. 9).

The wires were removed on July 29, 1956, after six recording sessions.

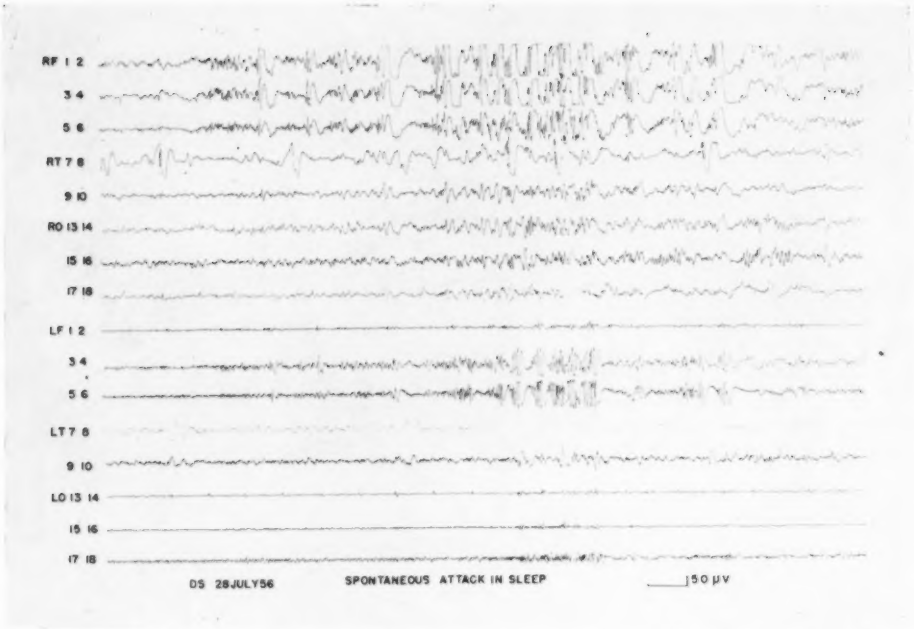
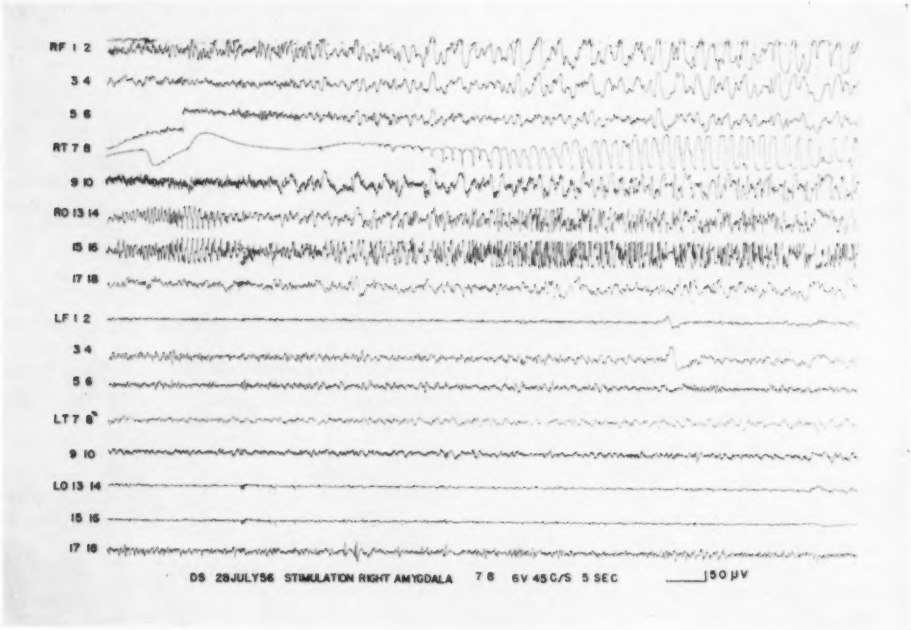


Fig. 8 (Case 2).—During sleep, high-voltage spiking, beginning in the right frontal region, occurred with independent bursts in the right amygdala (*RT 7-8*). The discharges spread to the right insula (*RT 9-10*), globus pallidus (*RO 13-14*), right internal capsule (*RO 15-16*), and left frontal region (*LF 3-4, 5-6*).

Fig. 9 (Case 2).—Stimulation of the right amygdala resulted in widespread after-discharge, chiefly unilateral, in the frontal region, insula, globus pallidus, and internal capsule, persisting for 40 seconds. There was no clinical evidence of this seizure.



Comment

Localization of Subcortical Spiking in Temporal Lobe Epilepsy.—The location of spikes in the cases studied here is definitely biased by reason of the position of the depth electrodes. An adequate sampling of the subcortical structures and the cortex has not been made. Accordingly, the findings, as might be expected, are mainly confined to the temporal and frontal lobes. In this series there were three patients who, at the time of the temporal spikes, had simultaneous discharges in the frontal region, usually on the inferior surface of the frontal lobe. One patient had spiking in the insula and two in the cingulum, either posteriorly near the splenium of the corpus callosum or, in one instance, at the rostrum of the corpus callosum. In one patient there appeared to be spiking in the hippocampus in association with a seizure which originated further anteriorly in the temporal lobe. These discharges occurred simultaneously with those on the surface or in the depth of the temporal lobe, and presumably were due to transmission from one area to another. Which was the primary discharging focus in these instances is impossible to say from the present recording techniques, since the discharges appeared almost simultaneously.

Spontaneous Independent Discharges in Extratemporal Structures.—In four patients suspected of having temporal lobe epilepsy, subcortical discharges were found in depth recordings entirely unassociated with discharges in the temporal region. Three of these patients had what would be considered fairly typical temporal lobe seizures, initiated by an epigastric aura or a confused feeling, associated with major convulsive seizures. The fourth patient had a rather atypical story in that he had merely a sensation of tension and tingling all over the body and at no time had a major convulsive attack. In these four patients discharges were found in the following structures: the orbital gyri, the frontal cortex, the frontal operculum, the caudate nucleus, the thalamus, the white matter of the internal capsule and centrum semiovale, and the insula. Each of these regions gave rise to spontaneous discharges quite independent of any firing in temporal structures. It should be noted that with none of these spontaneous discharges, some of which lasted for several seconds, was there the aura associated with the patient's usual convulsive episodes, or other overt manifestation of the subcortical discharge. In some instances the spontaneous discharges occurred while a temporal lobe focus was firing and appeared to be quite independent of it.

Relationship of Spontaneous Temporal Spiking to Clinical Phenomena.—The long examination of the subcortical discharges and activity in patients with temporal lobe epilepsy has demonstrated that bursts of temporal lobe firing lasting for seconds, or sometimes minutes, may occur without any overt manifestation of a clinical spell. In many of these episodes the patient may respond and talk during such a burst of activity, which may or may not be altered by the thought processes and verbalization of the patient. However, similar electrographic fits may develop, at times, into the usual attack of the patient, as has been observed in two cases. Yet the great majority of spontaneous electroencephalographic bursts in the temporal lobe occur without the production of any overt clinical phenomena.

Functional Correlates of Spontaneous Bursts in the Temporal Lobe.—During the interictal spiky activity of the temporal cortex and subcortical structures, is there an abolition of, or interference with, the normal activity of the temporal lobe, or do these epileptic-like discharges occur with the preservation of normal function of the involved area? The patients studied seemed to comprehend, think, and speak normally at the time of spike sequences. Complex examinations of neural function, such as Delgado and Hamlin's recordings,[2] do not bring out a consistent relationship of the electrical bursts and mentation.

Threshold for After-Discharge of Temporal Lobe Structures.—Stimulation of the

TABLE 2.—*Thresholds for After-Discharge of Temporal Lobe and Associated Structures*

	Strength of Stimulation					
	Under 5 Volts			5-10 Volts		
	No. of Stimulations	No. of Clinical Responses	No. and Percentage of After-Discharges	No. of Stimulations	No. of Clinical Responses	No. and Percentage of After-Discharges
Amygdala	49	1	15 (30%)	44	2	18 (40%)
Hippocampus	54	1	11 (20%)	10	1	9 (90%)
Temporal lobe (cortex & white matter)	97	1	11 (11%)	18	1	4 (22%)
Insula	46	1	6 (13%)	21	7	7 (33%)
Uncus (including pyriform cortex and perforated space)	7	0	0	29	7	9 (39%)
Cingulate gyrus	41	0	3 (7%)	19	0	10 (52%)

superficial and deep structures of the temporal lobe was routinely carried out through the depth electrodes. On the basis of these stimulations one may gain some idea of the threshold for after-discharge of the various temporal lobe structures. The thresholds, expressed in volts, are not comparable to those obtained by bipolar electrodes placed upon the surface of the temporal lobe because of the difference in the resistance between the cortical and the subcortical electrodes, respectively. At times the resistance between the depth leads was as low as 40,000 ohms but at other times might be 200,000 ohms, whereas the resistance between surface electrodes is rarely more than 10,000 ohms. Such marked variations would modify the current, and hence vary the strength of stimulation. This factor makes the following data on the thresholds of only relative value.

In the 14 patients in this series, 1,264 stimulations were made. In Table 2 are given the data relative to the responses of the various temporal lobe structures.

From these data those cases have been eliminated in which two structures might have been stimulated by the current. In many cases the voltage was considerably less than the arbitrary upper limits used in the Table. For example, on many occasions the hippocampus or amygdala might be fired with a stimulus of 3 volts. However, for purposes of compilation, all stimuli of 5 volts or under have been grouped together and those from 5.1 to 10 volts are independently considered. An after-discharge was considered present if spiking persisted after stimulation at the site of the excitation for at least two seconds. A clinical response was defined as any type of motor or sensory phenomenon noted by the patient or observed during or immediately subsequent to the stimulation. In all but two or three instances the phenomena were sensory and were attested to by the patient at the conclusion of the stimulation.

It is apparent from inspection of Table 2 that the threshold for excitation of the amygdala and hippocampus is definitely lower than that for the other structures of the temporal lobe and cingulate gyrus. Whether the hippocampus has a lower threshold than the amygdala, or vice versa, cannot be determined with certainty from this study. The differences between the thresholds under 5 volts would seem to be insignificant. The slightly lower threshold for the amygdala is not borne out in the stimulations over 5 volts.

It should be pointed out that such low-threshold areas may not represent epileptogenic foci, or even be an anatomical substrate of the convulsive pattern. In fact, as we have noted, their excitation may be accompanied by phenomena unlike the aura of the usual attack, even though spontaneous attacks may begin with localized spiking in the area.

Clinical Responses Induced by Temporal Lobe Stimulation.—I. Sylvian Region, Including the Insula and Operculum: Upon electrical stimulation of the Sylvian region the following responses have been noted: confusion, interruption of thought, arrest of speech, hunger, and epigastric sensations, including nausea.

II. Amygdala: Phenomena related to both corporeal and psychic states were produced by stimulation of the amygdaloid complex. Somatic sensations—paresthesias of the contralateral side of the body and pain in the entire side—were noted by two patients, one of whom identified the paresthesias with his aura. Visceral sensations—nausea and gustatory sensations—were induced in two patients. Twitching of the limbs with or without involvement of the face occurred in two patients. Psychic phenomena were induced in two patients. In one patient mental confusion and a sense of impending doom occurred with the stimulation of the nucleus, and in the other case there was a premonition that the usual aura of "tremor" was going to develop.

III. Hippocampus: Both somatic and visceral sensory, motor, and psychic phenomena developed upon stimulation. One patient had an epigastric aura reproduced.

Fig. 10.—Patient had attacks of hiccupping, followed by a generalized seizure; his electroencephalogram had generalized disturbances, which were less marked during sleep. Repeated stimulation of the electrodes in the anterior perforated space and insula (*RT-7-8*) consistently induced an unpleasant epigastric sensation, with impaired responsiveness, associated with diffuse discharges in the right temporal lobe, right frontal, thalamic, and caudate traces.

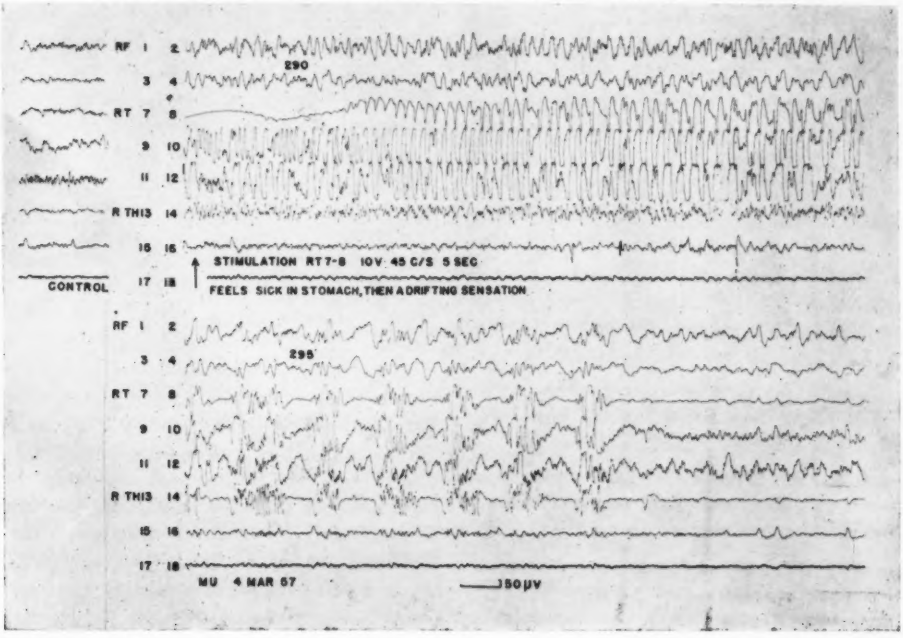
The leads are as follows:

RF tress: 1, orbital gyrus near olfactory tract; 2, white matter above orbital gyrus; 3, white matter above orbital gyrus; 4, white matter in front of anterior horn; 5, white matter in front of anterior horn; 6, white matter in front of anterior horn.

LF tress: 7, olfactory tract; 8, orbital gyrus or white matter above; 9, white matter; 10, white matter; 11, white matter; 12, white matter.

RTH tress: 13, lateral margin mesencephalon; 14, nucleus ventralis posterolateralis; 15, nucleus ventralis posterolateralis and lat. posterior; 16, tail of caudate nucleus; 17, white matter, semiovale; 18, white matter, semiovale.

RT tress: 7, anterior perforated space—insula; 8, insula above amygdala; 9, putamen; 10, insula; 11, sylvian cortex, superior temporal gyrus; 12, sylvian cortex, superior temporal gyrus.



Paresthesias occurred in the ipsilateral extremities in one patient and in the contralateral extremities in another. One patient turned the head to the side of stimulation. In one patient, as the hippocampus was stimulated to after-discharge, confusion developed.

IV. Anterior Perforated Space: Olfactory hallucinations occurred on three occasions from stimulation of the anterior perforated space, and gustatory phenomena once. In one patient on different occasions the following phenomena were induced: occipital pain, respiratory arrest, and epigastric pain or cramp (Fig. 10).

V. Other Subcortical Areas: Pain or paresthesias in the contralateral hand or entire side of the body occurred in three patients upon thalamic stimulation. Stimulation of the parietal white matter induced "lights in the (contralateral) eye," and, on another occasion, deafness in one patient. Pain in the contralateral extremities was noted on stimulation of the globus pallidus and internal capsule in two patients, accompanied by movements of the eyelids or limbs. On many occasions the frontal white matter was stimulated, but only once was a clinical response obtained—a sensation of abdominal cramps.

Site of Induced Hallucinations.—Somatic Sensations: Stimulation of the amygdala (two cases), hippocampus (two cases), and thalamus (two cases) induced peculiar sensations in the contralateral half of the body, described as numbness or "a feeling." Painful dysesthesias were induced from excitation of the thalamus (two cases), amygdala (one case), and globus pallidus and/or internal capsule (three cases).

Taste: Gustatory hallucinations were induced from the amygdala (one case) and anterior perforated space (one case).

Olfactory Sensations: Smells were induced only in one patient, upon stimulating the anterior perforated substance.

Epigastric Sensations: Nausea, abdominal sensations, hunger, and cramps have occurred upon stimulation of the anterior perforated space, amygdala, insula, and frontal white matter.

Other motor and sensory phenomena were elicited on isolated occasions from stimulation of the deep temporal structures and basal ganglia, as noted above.

It is noteworthy that relatively few stimulations, and only those producing after-discharge, gave rise to clinical phenomena. In fact, out of almost 150 stimulations of the amygdala and hippocampus, only 5 of the 53 producing after-discharge gave rise to clinical phenomena. However, from the insular and uncal stimulation, the incidence of clinical phenomena seemed to be considerably higher, especially when stronger strengths of stimuli were used. The sensory phenomena elicited by insular or uncal stimulation were largely related to visceral hallucinations, such as a cramp in the stomach or an epigastric feeling. This does not imply that the clinical phenomena elicited on stimulation were necessarily the auras of the patients' attacks. In fact, in most instances the phenomena were denied by the patients as being typical of the aura associated with their convulsive episodes.

Spread of After-Discharge to Other Subcortical Structures from Temporal Lobe Stimulation.—The propagation of discharges from the temporal lobe seems to be quite extensive. From the amygdala, discharges were picked up in the putamen, insula, internal capsule, orbital gyri, globus pallidus, superior temporal gyri, hippocampus, and cingular gyrus, as well as in the contralateral insula. From the insula, discharges were found in the putamen, superior temporal gyrus, orbital gyri of the frontal lobe, and frontal white matter; in the ventroposterior nucleus of the thalamus and lateral mesencephalic regions, and in the contralateral cingular gyrus and contralateral internal capsule. From the hippocampal gyri, discharges were present in the fusiform gyrus and the middle and superior temporal gyri. It is therefore apparent that the dissemination of after-discharge as the result of electrical stimulation of the temporal lobe structures, both on the surface

and deep, is quite wide. From this study no indication may be obtained as to the preferential pathways of the discharge.

Significance of Induced After-Discharge.

It is apparent from a rather casual perusal of the data given here that an after-discharge associated with clinical phenomena may be obtained from many parts of the temporal lobe. The hallucinations induced by the electric current may or may not be those commonly noted by the patient in association with the epileptic attack. In fact, more frequently than not, the phenomena induced are foreign to the aura of the attack. It must, therefore, be assumed that an after-discharge in the temporal lobe is not necessarily indicative of an epileptogenic area. The question might then be asked whether the point from which an aura is produced represents the epileptogenic focus. While this seems a likely conclusion, it must be admitted that the final proof of this assumption is lacking, since it is quite possible that one might be stimulating fibers coming from or going to an area responsible for the epileptic seizure. Difficulties may arise in determining that an aura has been reproduced. In particular, minor lapses of consciousness may be hard to evaluate, for electrical stimulation of depth electrodes may cause arrest of speech and mentation without inducing the actual attack of the patient. In one patient during stimulation of the temporal lobe there was cessation of spontaneous conversation and unresponsiveness. However, at the conclusion of the stimulation, the patient stated that he was aware of what was going on, but had been suffering an abdominal cramp or sensation, with which he was so intensely preoccupied that he could not answer questions.

Correlation of Clinical, Electrographic, and Surgical Results.—Of the 14 patients studied, 7 had characteristic psychomotor seizures and temporal spike foci; 5 had such clinical seizures but diffusely abnormal surface recordings, and 2 had a history of bizarre seizures with unconsciousness and normal surface electroencephalograms.

Of the first group, focal abnormalities were found in depth recordings from the temporal lobe in four cases. In two cases, stimulation of actively discharging points mimicked or reproduced the spontaneous fit, as was described by Penfield [5] and others in records made at the operating table. Of the four patients, three subsequently underwent temporal lobectomy. Two have had no seizures, though occasional aurae are noted and some spikes are seen in the electroencephalogram. In the remaining three patients, diffuse subcortical abnormalities, such as were described by Meyers [4] and Hayne [3] and their associates, and by others, were encountered, but no typical seizures could be elicited. One patient, previously subjected to bilateral temporal lobectomy because of persistent seizures with bitemporal spike foci, had bilateral frontal and right temporal high-voltage spiking and slowing.

In the second group, five patients with psychomotor seizures had diffusely abnormal surface records and multiple diffuse spike discharges in depth recordings. One had a diffusely abnormal surface electroencephalogram with suppression of spikes during sleep. In the depth recordings, however, temporal and thalamic spikes were recorded only when the patient was asleep. Spontaneous attacks occurred in the subcortical structures both in sleep and while awake without clinical concomitants. In this group, numerous electrical and/or clinical phenomena were elicited upon stimulation without reproducing the aura of the attack. One patient had a temporal lobectomy without relief of seizures.

The particular value of depth recordings may be illustrated by the consideration of one patient.

For three years this patient had had attacks of various types, described as "nightmares, tremors, shakes, or freezing." These episodes all were initiated by a sudden arrest of activity and "freezing in a certain position" for a few seconds without impairment of consciousness. The "shakes" were preceded by a peculiar smell, which was not always the same, and the tremors—the most annoying type of attack—were described as a "very funny feeling running throughout my body when

there's a lot of tension." Phenobarbital and diphenylhydantoin relieved the attacks, except for the tremors.

In the electroencephalogram a right temporal spike, sometimes conducted to the left temporal region, was consistently present. Recording was made from six sets of six-filament depth electrodes in the frontal, temporal, and parieto-occipital regions.

Electrical stimulation of the deep electrodes induced local after-discharge but no clinical manifestations suggestive of the patient's usual attacks. During the recording, several clinical spells occurred without electrographic concomitants. The intravenous injection of 200 mg. of pentylenetetrazol produced after three minutes a "sensation" on the left side, spiking in the right hippocampus-amygdala leads, and, slightly later, "an awful smell."

Because the subcortical discharges were not temporally related to the clinical attacks, and subcortical stimulation of the deep temporal structures did not elicit the "tremors or shakes," it was concluded that the spells were not related to the abnormal temporal lobe activity. A psychiatric opinion was requested. Dr. Harold Rosen concluded that the diagnosis was "an hysterical reaction in an extremely passive-dependent patient whose latent homosexuality is pronounced and with which, he is at present, unconsciously in an almost constant struggle."

Summary

Depth recording allows:

1. The induction of the electrical and clinical fit in certain patients, thus adding further evidence of the focal temporal origin of the seizure.

2. The examination of the subcortical activity over a period of time, during which diffuse or focal discharges may occur associated with or independent of clinical phenomena.

3. The mapping out of the thresholds for after-discharge of subcortical tissue, which may indicate foci of marked irritability, with or without focal spontaneous spiking.

4. The induction of the clinical seizure by chemical means while the electrical activity is being sampled at many points.

On the basis of these findings, certain patients may be advised to have temporal lobectomy and others discouraged because of the probability that their attacks arise from extratemporal structures.

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Serum Lipid and Cholesterol Levels in Cerebrovascular Disease

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Vascular disease of the brain is an important cause of death and disability in the United States. Recently it has been estimated that there are 2,000,000 people in the United States who are suffering from this condition.[1] As a result, there has been increasing interest in the treatment of circulatory insufficiency resulting from atherosclerosis of the major cerebral vessels, since this is the commest single cause of neurological deficit. At present, therapeutic measures are directed toward maintenance of optimum blood pressure and cardiac output, prevention of embolization, and improvement of the collateral circulation by means of anticoagulant drugs or by surgical reconstruction of atherosclerotic carotid and vertebral arteries.[2-10] Prevention or arrest of atherogenesis must await a more complete understanding of its cause.

Numerous studies have been reported of serum lipid and cholesterol levels in patients suffering from atherosclerosis of the coronary arteries and aorta, but we have been unable to find reports of serum lipid and cholesterol levels in a large group of patients suffering from well-documented vascular disease of the brain.

The purpose of this paper is to report a statistical analysis of serum cholesterol and lipid determinations in 110 patients admitted to the neurological service of the Receiving Hospital of the City of Detroit with a diagnosis of cerebrovascular disease. These determinations were compared with two separate "control' groups: (1) A group of 79 patients of comparable age who were admitted to the same wards for nonvascular neurological disease (Group 4). (2) A group of 22 men having an average of 30 years who are believed to be in good health (Group 2). This group was composed of medical staff, students, and technicians.

In addition, the data were analyzed for the racial incidence of various types of cerebrovascular disease, the incidence of diabetes mellitus, the incidence of hypertension, and the relative frequency of atherosclerotic involvement of various vessels.

Material and Methods

Blood samples were drawn in the fasting state, and serum cholesterol and lipid values were determined by methods described by one of us (B. Z.) previously.[11-13] These methods have been used in the clinical chemistry laboratories of the Detroit Receiving Hospital for five years, and wide experience has been gained of its use in several thousand cases. To establish the accuracy of the determinations at the Detroit Receiving Hospital, a second laboratory was established by the departments of neurology and pathology at Wayne State University College of Medicine. Independent determinations were made on the same samples in 60 patients by the two laboratories. Serum cholesterol determinations regularly showed agreement within 10 mg. %.[14] Serum lipids showed a wider variation in the results obtained, but, with a few exceptions, the range of variation did not exceed 50-100 mg. %.*

The experimental group comprised 110 consecutive and unselected patients admitted to the neurological service of the Detroit Receiving Hospital with a diagnosis of cerebrovascular disease (Group 5). The diagnosis was established by care-

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* Miss Phylliss Harrison, fourth-year medical student, performed the 60 separate cholesterol and lipid determinations.

ful history, medical and neurological examinations, electroencephalography, and lumbar puncture. The clinical diagnosis was confirmed by carotid or vertebral angiography in 56% of this group of patients † and by necropsy in an additional 2.3%. In addition, this group of 110 cases of all types of cerebrovascular disease was subdivided according to diagnosis. There were 12 cases of subarachnoid hemorrhage due to ruptured aneurysm or vascular malformation (Group 7), 7 cases of hypertensive encephalopathy, and 1 case of cerebral polyarteritis nodosa (Group 8). There were 31 cases of vertebral-basilar artery insufficiency (Group 12) and 28 cases of insufficiency of the internal carotid arteries (Group 13). The remaining 31 cases (Group 10) were of atherosclerosis of the smaller cerebral vessels (middle, anterior, and posterior cerebral vessels and their branches).

For convenience in tabulation, the disease in Group 12 (vertebral-basilar artery insufficiency) and in Group 13 (carotid artery insufficiency) will be referred to as "large-vessel disease," and that in Group 10 (disease of middle, anterior, and posterior cerebral vessels and their branches) will be referred to as "small-vessel disease." The combination of Groups 10, 12, and 13 are therefore believed to constitute a group with cerebrovascular disease due to atherosclerosis (Group 9).

Results

The data concerned with serum cholesterol and lipids have been analyzed in two ways.

1. The mean serum values of the experimental and control groups were compared (Tables 1 and 3).

†Dr. Sheila Sheehan performed the angiographic examinations.

2. The numbers of individual patients in each group were compared who had serum values elevated above figures generally accepted to be normal (Tables 2 and 4). Since a majority of patients in the experimental group had determinations made on more than one blood sample, this latter analysis was extended to include (*a*) the number of patients whose individual average serum level was elevated, and (*b*) the number of patients who had an elevated serum level on at least one determination.

None of the mean serum cholesterol values of any of the groups of patients with cerebrovascular disease were found to show a significant difference from the values found in patients of comparable age with nonvascular disease (Group 4, Table 1). The mean serum cholesterol value for the group of healthy young men (Group 2) was significantly different from the value for patients with ruptured aneurysm or malformation (Group 7) and from that for Group 6, which includes the patients with hypertensive encephalopathy and arteritis. In other respects, however, our group of patients with cerebrovascular disease did not show mean values of serum cholesterol which were significantly different from the value for healthy young men.

In order to analyze the number of individual patients with elevated serum cholesterol values, three different "normal

TABLE 1.—*Comparison of Mean Cholesterol Levels*

Group	Diagnosis	Mean Cholesterol, Mg. %	No. Cases	Mean Age	Range of Cholesterol, Mg. %	Standard Deviation
1	Total cases	255	211	49.5	109-408	48.3
2	Healthy men	244	22	30.0	200-300	25.4
3	All neurological disease	257	189	51.8	109-408	49.0
4	Neurological disease other than vascular	257	79	46.8	109-408	54.5
5	All cerebrovascular disease	257	110	55.5	148-399	47.0
6	Cerebrovascular disease: Group 7 plus Group 8	278 *	20	43.5	161-357	55.0
7	Ruptured aneurysm or malformation	279 *	12	42.5	194-357	51.2
8	Hypertensive encephalopathy and arteritis	276	8	45.0	161-340	59.5
9	Cerebrovascular disease due to atherosclerosis (Groups 10 and 11)	255	90	58.2	148-399	45.0
10	Small-vessel disease	254	31	57.5	171-339	13.0
11	Large-vessel disease (Groups 12 and 13)	252	59	58.7	148-399	47.0
12	Vertebral-basilar insufficiency and/or occlusion	259	31	61.2	189-399	44.0
13	Carotid insufficiency and/or occlusion	244	28	56.0	148-348	49.0

* Statistically significant elevation when compared with Group 2 (95% level of confidence).

TABLE 2.—*Comparison of Number of Cases with Elevated Cholesterol Levels*

Group	Diagnosis	No. Cases	Mean Age	"Normal" Level, Mg/100 Cc.	One Value Elevated	Average Elevated
1	Total no. cases	211	49.5	260	100 (47.4%)	82 (38.8%)
				275	82 (38.8%)	67 (31.8%)
				300	53 (25.1%)	41 (19.4%)
2	Healthy men	22	30.0	260	6 (27.2%)	6 (27.2%)
				275	3 (13.6%)	3 (13.6%)
				300	0	0
3	All neurological disease	189	51.8	260	94 (49.7%) *	76 (40.2%)
				275	79 (41.8%) *	64 (33.9%)
				300	53 (28.0%) *	41 (21.7%) *
4	Neurological disease other than vascular	79	46.8	260	36 (45.5%)	32 (40.5%)
				275	29 (36.8%) *	26 (32.9%)
				300	18 (22.8%) *	18 (22.8%) *
5	All cerebrovascular disease	110	55.5	260	58 (52.7%) *	44 (40.0%)
				275	50 (45.4%) *	38 (34.5%)
				300	35 (31.8%) *	23 (20.9%) *
6	Cerebrovascular disease: Group 7 plus Group 8	20	43.5	260	14 (70.0%) *	12 (60.0%) *
				275	14 (70.0%) †	11 (55.0%) *
				300	13 (65.0%) †	9 (45.0%) †
7	Ruptured aneurysm or malformation	12	42.5	260	9 (75.0%) *	7 (58.3%)
				275	9 (75.0%) †	7 (58.3%) *
				300	9 (75.0%) †	6 (50.0%) *
8	Hypertensive encephalopathy and arteritis	8	45.0	260	5 (62.5%)	5 (62.5%)
				275	5 (62.5%) *	4 (50.0%) *
				300	4 (50.0%) *	3 (37.5%) *
9	Cerebrovascular disease due to atherosclerosis (Groups 10 and 11)	90	58.2	260	44 (48.9%)	32 (35.6%)
				275	36 (40.0%) *	27 (30.0%)
				300	22 (24.5%) *	14 (15.6%) *
10	Small-vessel disease	31	57.5	260	15 (48.4%)	11 (35.5%)
				275	13 (41.9%) *	10 (32.2%)
				300	9 (29.0%) *	4 (12.9%)
11	Large-vessel disease (Groups 12 and 13)	59	58.7	260	29 (49.2%)	21 (35.6%)
				275	23 (39.0%) *	17 (28.8%)
				300	13 (22.0%) *	10 (17.0%) *
12	Vertebral-basilar artery insufficiency and/or occlusion	31	61.2	260	16 (51.5%)	13 (41.9%)
				275	13 (41.9%) *	10 (32.3%)
				300	8 (25.8%) *	6 (19.4%) *
13	Carotid artery insufficiency and/or occlusion	28	56.0	260	13 (46.4%)	8 (28.6%)
				275	10 (35.7%)	7 (25.0%)
				300	5 (17.8%)	4 (14.3%)

* Statistically significant elevation when compared with Group 2 (χ^2-test; $P<0.05$, or 95% level of confidence).
† Statistically significant elevation when compared either with Group 2 or with Group 4.

cholesterol levels" were selected. A level of 260 mg. % is considered as the upper limit of normal at Detroit Receiving Hospital, but the data were also analyzed using 275 and 300 mg. % as the upper limit of normal, since there is not universal agreement by investigators on what constitutes a "normal" value. Table 2 reveals that a significantly greater per cent of patients with cerebrovascular disease had an abnormally high serum cholesterol value when compared with healthy young men. This was especially true if the higher values (275 and 300 mg. %) were considered the upper limits of normal and if patients with at least one elevated value were compared, rather than the patients with an elevated average level. However, the group of patients with nonvascular neurological disease (Group 4) also contained a significantly greater per cent with abnormal cholesterol levels. Furthermore, the per cent of patients in this group with an elevated cholesterol level was not found to differ significantly from the per cent occurring in the group with cerebrovascular disease, with the exception of those with subarachnoid hemorrhage, hypertensive encephalopathy, and arteritis (Groups 6 and 7).

TABLE 3.—*Comparison of Mean Lipid Levels*

Group	Diagnosis	Mean Lipid, Mg. %	No. Cases	Mean Age	Range of Lipid, Mg. %	Standard Deviation
1	Total cases	754	136	46.1	428-1,493	168
2	Healthy men	578	22	30.0	464-838	77.6
3	All neurological disease	788 *	114	49.2	428-1,493	181
4	Neurological disease other than vascular	767 *	100	45.9	428-1,170	155
5	All cerebrovascular disease	807 *	61	52.1	471-1,493	201
6	Cerebrovascular disease: Group 7 plus Group 8	851 *	15	40.9	622-1,170	164
7	Ruptured aneurysm or malformation	859 *	10	41.1	645-1,170	189
8	Hypertensive encephalopathy and arteritis	833 *	5	40.6	622-913	109
9	Cerebrovascular disease due to atherosclerosis (Group 10 and 11)	793 *	46	55.8	471-149	212
10	Small-vessel disease	765 *	16	55.8	513-1,047	148
11	Large-vessel disease	808 *	30	55.8	471-1,493	238
12	Vertebral-basilar artery insufficiency and/or occlusion	863 *	17	58.4	590-1,462	227
13	Carotid artery insufficiency and/or occlusion	736 *	13	52.7	471-1,493	253

* Statistically significant elevation when compared with Group 2 (95% level of confidence).

Analysis of the serum lipid determinations revealed a different pattern. All groups with cerebrovascular disease had a mean serum lipid level which was significantly higher than that of the group of healthy controls (Group 2, Table 2). However, the mean serum lipid level of the group of patients with nonvascular disease (Group 4) was also significantly higher that that of Group 2, and there was no difference in mean serum lipid levels between neurological patients with and those without cerebrovascular disease, regardless of type (Table 3).

The number of patients with abnormally high lipid levels (above 1,100 mg. %) were fewer than those with abnormally high cholesterol levels in all groups. There was no significant difference between the per cent with abnormal lipid levels in the group of healthy young male subjects (Group 2) and the group of neurological patients without symptomatic cerebrovascular disease (Group 4, Table 4). There were significantly more patients with elevated values in the group with cerebrovascular disease than in the group of healthy young men (Group 2), but only the groups with subarachnoid hemorrhage (Group 7) and with basilar artery insufficiency or occlusion (Group 12)

TABLE 4.—*Comparison of Number of Cases with Elevated Lipid Levels* *

Group		No. Cases	Mean Age	One Value Elevated	Average Elevated
1	Total cases	136	46.1	18 (13.2%)	8 (5.9%)
2	Healthy men	22	30.0	0	0
3	All neurological disease	114	49.2	18 (15.8%) †	8 (7.0%)
4	Neurological disease other than vascular	53	45.9	7 (13.2%)	2 (3.8%)
5	All cerebrovascular disease	61	52.1	11 (18.0%) †	6 (9.8%)
6	Cerebrovascular disease: Group 7 plus Group 8	15	40.9	4 (26.7%) †	2 (13.3%)
7	Ruptured aneurysm or malformation	10	41.1	3 (30.0%) †	2 (20.0%) ‡
8	Hypertensive encephalopathy and arteritis	5	40.6	1 (20.0%)	0
9	Cerebrovascular disease due to atherosclerosis (Group 10 and 11)	46	55.8	7 (15.2%) †	4 (8.7%)
10	Small-vessel disease	16	55.8	2 (12.5%)	0
11	Large-vessel disease (Group 12 and 13)	30	55.8	5 (16.7%) †	4 (13.3%)
12	Vertebral-basilar artery insufficiency and/or occlusion	17	58.4	4 (23.5%) †	3 (17.7%) ‡
13	Carotid artery insufficiency and/or occlusion	13	52.7	1 (7.7%)	1 (7.7%)

* Normal 1,100 mg. %.

† Statistically significant elevation when compared with Group 2 (χ^2-test; $P<0.05$, or 95% level of confidence).

‡ Statistically significant elevation when compared either with Group 2 or with Group 4.

TABLE 5.—*Incidence of Hypertension in Cerebrovascular Disease*

Group	Diagnosis	No. of Patients	No. with Hypertension	Per Cent
4	Neurological disease other than vascular	79	3	3.8
5	All cerebrovascular disease	110	45	40.9
6	Cerebrovascular disease due to hypertensive encephalopathy, arteritis, ruptured aneurysm, or malformation	20	17	85.0
7	Ruptured aneurysm or malformation	12	9	75.0
8	Hypertensive encephalopathy and arteritis	8	8	100.0
10	Small-vessel disease	31	13	41.9
11	Large-vessel disease	59	15	25.4

contained a greater per cent of patients with elevated values than did Group 4.

Diabetes mellitus was found to be commoner in cerebrovascular disease than in other neurological diseases (Table 5), but this did not significantly affect the mean cholesterol or lipid values of the groups. It should be noted, however, that all the diabetics were in metabolic control by the use of diet and/or insulin and showed no evidence of ketosis. Hypertension was likewise commoner in cerebrovascular disease (Table 6), particularly in association with ruptured aneurysm or malformation (Group 7); in this small group 75% of patients suffered from hypertension, and our clinical experience with a larger group of cases with ruptured aneurysm or malformation supports this high incidence of associated hypertension. The entire patient population studied (Group 1) was 60.3% Negroes. This permitted a comparison of the racial incidence of the various types of cerebrovascular disease and of serum lipid and cholesterol levels. It was found that the incidence of all types of cerebrovascular disease, including internal carotid and vertebral-basilar artery insufficiency, was not different in white and in Negro groups. Nor was any racial difference noted in the serum cholesterol or lipid levels.

TABLE 6.—*Incidence of Diabetes Mellitus in Cerebrovascular Disease*

Group	Diagnosis	No. of Patients	No. with Diabetes	Per Cent
4	Neurological disease other than vascular	79	5	6.3
5	All cases of cerebrovascular disease	110	14	12.7
6	Cerebrovascular disease due to hypertensive encephalopathy, ruptured aneurysm, or malformation	20	3	15
9	Cerebrovascular disease due to atherosclerosis	90	11	12.2

It is of interest that in this group of 90 consecutive, unselected cases of atherosclerotic cerebrovascular disease, 31 patients suffered from predominantly vertebral-basilar artery disease, 28 from carotid artery disease, and 31 from disease of other smaller vessels.

TABLE 7.—*Racial Incidence of Types of Cerebrovascular Disease*

Group	Diagnosis	Per Cent	
		White	Negro
3	All cases of neurological disease	39.7	60.3
4	Neurological diseases other than vascular	43	57
5	All cases of cerebrovascular disease	37.3	62.7
6	Cerebrovascular disease due to hypertensive encephalopathy, arteritis, ruptured aneurysm, malformation	35	65
10	Small-vessel disease	41.8	58.2
11	Large-vessel disease	35.6	64.4
12	Vertebral-basilar artery insufficiency	35.5	64.5
13	Internal carotid artery insufficiency	35.7	64.3

Comment

There is indirect evidence from epidemiological, experimental, clinical, and biochemical studies that the quality and quantity of dietary fats influence the development of atherosclerosis.[15] The evidence supporting the view that lipids are involved in the pathogenesis of atherosclerosis is derived from four general areas: observations of the high lipid content of human atherosclerotic plaques; the production and modification of arterial lesions in animals resembling those

of human atherosclerosis by experiments designed to affect the lipid metabolism; the observation of the high frequency of atherosclerosis in human subjects suffering from diseases characterized by hyperlipemia, and observations of variations in the occurrence of atherosclerosis in various population groups subsisting on diets of varying lipid composition.[16]

Studies of cholesterol and β-lipoprotein fractions of serum lipids in patients with atherosclerosis of the coronary arteries with myocardial infarction have shown a slight increase in mean values, as compared with groups of normal subjects of comparable age.[17,18] Necropsy studies have failed, however, to establish any discernible relation between the level of serum lipid fractions and the severity of the atherosclerotic process.[19,20]

There is indirect evidence to support the view that cerebral atherosclerosis, in its pathogenesis, is similar to, if not identical with, coronary atherosclerosis, since pathological and clinical reports show a close association between atherosclerosis of the cerebral and coronary vessels.[21-23] However, studies of lipid metabolism, such as that reported here, are important in the study of cerebral atherosclerosis, since the level of blood cholesterol may be controlled by the quantity and quality of fat in the diet.[24] It is possible that a low-animal-fat diet may be useful in the treatment and prevention of cerebral atherosclerosis, particularly since it has been shown experimentally that during postalimentary hyperlipemia there are increased blood viscosity, increased adhesiveness of the blood elements, and slowing of blood flow in small cerebral vessels.[25-28] In addition, there is some evidence that during postalimentary hyperlipemia there is a state of increased coagulability of the blood.[15,29,31]

The results of the present study do not reveal any significant difference in the mean serum cholesterol and lipid levels in 110 patients with cerebrovascular disease when compared with those of a group of hospitalized patients of comparable age with neurological disease other than vascular in nature. Furthermore, with the exception of the group of patients with ruptured aneurysm or malformation and hypertensive encephalopathy, the mean cholesterol levels were not significantly different from those of healthy young men. The group of patients with ruptured aneurysm or malformation had a high incidence of hypertension, a condition that is known to be associated with a statistically significant elevation of serum cholesterol levels.[32]

After analysis of the number of patients in each group with an abnormally high serum cholesterol value, it was found that there was a significantly greater per cent in the group with cerebrovascular disease and in the group of comparable age with nonvascular neurological disease than occurred in the group of healthy young men. It seems evident that in this series the increase in serum cholesterol and lipids in the two older age groups reflects the well-known tendency of these values to increase with age.[16] It probably does not indicate a more specific relation to the incidence of cerebral atherosclerosis.[1]

The data reported here indicate that advanced atherosclerosis of cerebral vessels commonly exists in the absence of significant elevation of serum cholesterol. This study does not exclude the possibility that in such cases hypercholesteremia may have been present at some time. As a matter of fact, we have studied several patients who were found to have normal serum cholesterol levels at the time of cerebrovascular symptoms but are known to have had an elevated serum cholesterol level in the past. Nor does this study exclude the logical probability that hypercholesteremia, when present, enhances any tendency toward atherosclerosis of cerebral vessels. The data also indicate that atherosclerosis of cerebral vessels usually becomes symptomatic at an age when there is a tendency toward elevation of serum lipid and cholesterol levels. Furthermore, many patients with cerebrovascular disease of all types have associated hypertension (Table 6) or a past

history of hypertension, a condition which is known to be associated with an increased incidence of hypercholesteremia, confirmed by the present study. In addition, it is common neurological experience that symptoms of atherosclerotic disease of cerebral vessels often become manifest when a previously elevated blood pressure has fallen to normal levels.[2]

Stamler [32] has questioned the validity of standards commonly accepted in the United States for normal plasma concentration of cholesterol. He has suggested the possibility that the habitual diet in the United States produces a chronic low-grade hypercholesteremia in millions of Americans. We have not excluded this possibility by the use of two "control" groups of different age. We have attempted to exclude other possible artifacts, such as changes due to age, hospital diet, and socioeconomic and racial factors. In addition, we have used three different "normal" values for serum cholesterol levels, the lowest of which we know from experience in the general hospital population is generally not exceeded, except in those diseases which are known to cause elevation of the serum cholesterol, such as myxedema, liver disease, nephrosis, and familial hypercholesteremia.

In this study, 12.7% of the patients with cerebrovascular disease suffered from associated diabetes mellitus. These diabetics were treated and did not show serum lipid or cholesterol values that were significantly different from the rest of the group with cerebrovascular disease uncomplicated by diabetes. In this particular series, the incidence of diabetes was twice that of a control group of comparable age. Since many of the group of comparable age were admitted because of neurological complications of diabetes (e. g., diabetic polyneuropathy), statistical comparison of the incidence of diabetes in the two groups is not reliable, and we believe the relative incidence of diabetes mellitus is actually higher than found in this study. As far as we have been able to determine, racial factors did not appear to influence the serum lipid values, the incidence of cerebrovascular disease, its manifestations or complications.

Atherosclerosis produces cerebral symptoms predominantly by involving three major groups of cerebral vessels with about equal frequency. In the group of patients reported here, approximately one-third showed evidence of disease in the vertebral-basilar arterial system; one-third had symptoms due to disease of the carotid arteries, and one-third had disease involving smaller cerebral vessels (anterior, middle, and posterior cerebral arteries and their branches). The high incidence of basilar and carotid artery disease in this series contrasts with the usual clinical impression of a much higher incidence of disease of the smaller vessels. This is due to several factors. Clinical syndromes due to occlusive disease of the vertebral-basilar and carotid arteries have been recognized only in the past few years, and recent advances in carotid, vertebral, and retrograde subclavian-vertebral angiography [37] have made confirmation of this diagnosis possible during life. In our experience with the evaluation of over 100 patients with cerebrovascular disease, cerebral angiography has proved helpful in planning therapy in many instances, and certainly has not proved to be harmful.

During the past year, we have advised our patients with cerebrovascular disease to follow a low-fat diet, since theoretically there is much to support this treatment, although its therapeutic usefulness is admittedly difficult to evaluate.

Summary

No significant difference has been found between the mean serum cholesterol or lipid determinations in a group of 110 patients with cerebrovascular disease and a group of hospitalized patients of comparable age with nonvascular neurological disease.

In this series, 12.7% of patients with cerebrovascular disease suffered from diabetes mellitus, but the diabetics (who are under therapeutic control) did not have serum lipid or cholesterol values that were significantly different from the rest of the group with

cerebrovascular disease uncomplicated by diabetes.

A group of patients with cerebral atherosclerosis involving the vertebral-basilar, internal carotid, or smaller cerebral arteries (i. e., anterior, middle, and posterior cerebral arteries and their branches) did not have mean lipid or cholesterol values that were significantly different from those of a group of healthy men having a mean age of 30 years; but there was a significantly greater per cent of patients with cerebrovascular disease who had elevated serum cholesterol or lipid values. This finding appeared to reflect the tendency of these values to increase with age.

A group of patients with developmental and/or diffuse hypertensive cerebrovascular disease (i. e., hypertensive encephalopathy, ruptured aneurysm, or malformation) were found to have significant elevations of serum cholesterol and lipid levels. Since 85% of this group of patients has associated hypertension, it is believed that hypertension may be the significant factor in relation to hypercholesteremia and hyperlipemia.

The incidence of all types of cerebrovascular disease, including carotid and vertebral-basilar artery insufficiency, was no different in white and Negro groups. Nor was any racial difference noted in serum cholesterol or lipid levels.

Atherosclerosis produces cerebral symptoms by involving three major groups of cerebral vessels with approximately equal frequency. Approximately one-third showed evidence of disease in the vertebral-basilar artery system; one-third had symptoms due to disease in the carotid arteries, and one-third to disease in the small cerebral vessels (anterior, middle, and posterior cerebral arteries and their branches).

In all types of cerebrovascular disease, the incidence of hypertension is significantly greater than in a group of comparable age with neurological diseases other than vascular in nature, in spite of the fact that atherosclerotic disease of cerebral vessels commonly manifests symptoms in the absence of hypertension or when a previously elevated blood pressure has fallen to normal levels.

Since hypercholesteremia and hyperlipemia probably enhance any tendency toward atherosclerosis of cerebral vessels, the therapeutic use of a low-fat diet in cerebrovascular disease is recommended.

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Cerebellar Pathology in an Infant Resembling Chick Nutritional Encephalomalacia

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Introduction

The neuropathological sequelae of feeding lipids high in linoleic acid in the absence of a satisfactory antioxidant (α-tocopherol) were discussed in the preceding report,[1] in which the feeding of corn oil or cottonseed oil was shown to increase the need for tocopherol. The relative tocopherol deficiency led to the production of gross cerebellar hemorrhages in the chick within two to four weeks. These vascular changes are preceded by shrinkage and disappearance of the Purkinje cells, and proliferation of the endothelium of the capillaries.

This paper will record a similar finding in the brain of an infant that had been given a commercial cottonseed oil preparation intravenously for 19 days, prior to her death, in order to combat a severe state of inanition that developed as a consequence of a rapidly growing abdominal tumor mass. This observation becomes significant in the light of the new knowledge of the mechanisms by which some unsaturated lipids promote the production of encephalomalacia in chicks. Such brain changes had not previously been observed during many years of routine examinations of human cerebella.

In a study designed to evaluate the tocopherol requirements of man, now in progress at the Elgin State Hospital, it has been observed that the lipids of the erythrocytes can be varied by altering the diet in its content of linoleic acid, which is one of the major components of some vegetable fats. For example, when 60 gm. of corn oil per day was fed to 25 men for prolonged periods, the amount of linoleic acid in the erythrocyte stroma, as determined by gas chromatographic techniques, was approximately twice as high as in 10 subjects who were receiving the regular hospital diet. Similarly, the brains of chicks fed equivalent amounts of corn oil from which the tocopherol had been removed showed marked increases in the linoleic acid content of their cerebellar tissue as compared with chicks fed coconut oil or oleic acid. Linoleic acid is peroxidized in vitro approximately 12 times as rapidly as oleic acid. Unless extra vitamin E is provided to prevent this peroxidation, chick encephalomalacia results when fats high in linoleic acid are fed. Corn oil contains about 55% linoleic acid.

Another related observation, noted in work now in progress, is that the peroxide hemolysis test, found to be positive in premature infants by György et al.[2] and by Gordon and De Metry,[3] and which is markedly increased in adult men eating unsaturated fats (Horwitt et al.[4]), can be related to the linoleic acid content of the erythrocyte. This peroxide-induced hemolysis can be prevented in vivo or in vitro by vitamin E, but the amounts needed seem to depend on the level of linoleic acid in the tissues.[5] The details of the gas chromatographic and hemolysis test techniques used, together with substantiating data obtained under conditions of precise dietary control, will be published elsewhere.

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Report of Case

Infant, 14 months of age at death; Research and Educational Hospital.

At the age of about 7 months the child had a bout of "flu," accompanied by nausea and vomiting and requiring hospitalization for four days. Following this episode, the child was less robust in her eating habits and more selective in her acceptance of foods. No real feeding problem was apparent to the mother until about six weeks to two months prior to her admission to the hospital. During this period she refused almost all foods and would accept only limited quantities of whole milk, cereals, and stewed prepared fruits. Prior to hospitalization, none of the vitamin supplements the child had received contained any tocopherol. According to the mother, the child did not lose weight prior to entering the hospital; but since the child had a rapidly growing, large tumor mass, with the accumulation of pleural fluid and ascites, her actual body weight, aside from the tumor and fluid, might actually have decreased considerably.

Two weeks prior to hospitalization the baby began to vomit all feedings uncontrollably. This persisted up to the time of admission. During the six weeks of her hospitalization she was also a severe nutritional problem. She went downhill, required feedings through a Levin tube and, finally, intravenous feedings consisting of 300 cc. of Lipomul,* 250 cc. of Aminosol (a modified fibrin hydrolysate), plus additional 5% dextrose in water each day from Aug. 20 to her death, on Sept. 9th. Lipomul contains 15% cottonseed oil, and this oil contains approximately 50% linoleic acid.

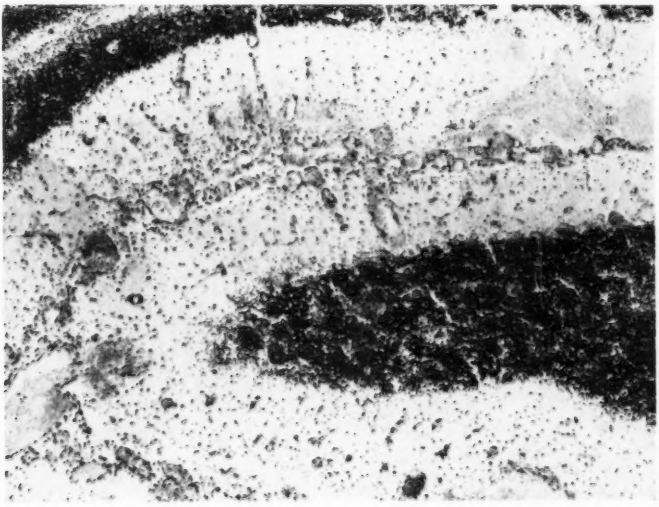
* Lipomul-Oral (Upjohn) is a 40% emulsion of vegetable oil in an aqueous carbohydrate medium.

A possible additional factor in the production of her cerebellar hemorrhages was the bone-marrow depression she was found to have in conjunction with her x-ray therapy of 1,800 r tumor dose to the abdomen and 1,200 r tumor dose to the chest. Her white cell count went from 15,000, on Aug. 29, to 2,150 on Sept. 8, 1958. The history of the vitamin preparations which had been provided to the child indicated that she had never had a tocopherol supplement.

At necropsy there was found a neuroblastoma of the right adrenal gland with metastases to the retroperitoneal lymph nodes, mediastinal lymph nodes, lower lobe of the right lung, and right parietal pleura. There were no intracranial metastases. The brain appeared normal on inspection and section except for the cerebellum, which seemed to be softer than normal, and reddish, as though not sufficiently hardened. Microscopic examination revealed no abnormalities in the cerebral hemispheres, but the cerebellum was the site of widespread hemorrhages, proliferation of the capillaries, and absence of the Purkinje cells (Figure).

Comment

The fact that structural lipids can be varied with relative ease by dietary means [5] may have far-reaching implications. Not only can adult tissue be altered by feeding unsaturated lipids but, since the structural fatty acids of fetal tissue are completely dependent on the diet of the mother, and tocopherol does not easily cross the placenta, unless relatively huge amounts are given the



Cerebellar folium. Note the proliferative endarteritis, hemorrhages, and absence of Purkinje cells. Klüver method.

mother (Minkowski et al.[6]), the finding of increased sensitivity to peroxide hemolysis in many infants [2,3] becomes more significant. One may recall the controversy of some years ago on the possible efficacy of vitamin E in preventing or curing retrolental fibroplasia in premature infants by Owens and Owens [7] and of the reports of the prevention of cerebromeningeal hemorrhages in prematures by Minkowski.[8] It is now apparent that the importance of vitamin E may be secondary to the amounts of peroxidizable fatty acids present in tissues exposed to oxygen, a variable which had not previously been considered. Vitamin E can slow down or prevent the peroxidation of linoleic acid in brain tissue [4] but cannot reverse such damage once it has occurred. Only very small amounts of vitamin E are necessary to protect animal tissue where the concentrations of linoleic acid in the diet are also low.[1] In evaluating this need for tissue antioxidant, it must be remembered that a normal diet usually has some linoleic acid in the fats ingested.

Important subtle changes in neural tissue may be involved as a consequence of alterations in lipid intake, which only additional research can uncover. In any case, interpretations of tissue-antioxidant needs should not be made without knowledge of the amount and type of unsaturated lipids that had been fed.

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A Study of Coagulation Factors in Blood and Spinal Fluid in Multiple Sclerosis

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Introduction

For over 90 years, since Charcot, a French neurologist, correlated the clinical and pathological changes associated with the disease designated as multiple sclerosis, many theories as to its etiology have been advanced. Theories pertaining to changes in vascular and blood factors are still controversial and consequently subjected to investigation. Changes in cerebrospinal fluid are also believed by many investigators to be of etiologic significance.

The following study was undertaken to determine whether the spinal fluid of normal subjects and/or of patients with multiple sclerosis has tissue and/or blood thromboplastic activity. Blood vessel fragility, coagulation factors, and platelets were investigated by current methods in cases of clinically well-established multiple sclerosis. The study also included evaluation of serum platelet-like activity and determination of sedimentation rates and cerebrospinal fluid protein levels.

Results obtained revealed that there is neither blood nor tissue thromboplastic activity in the spinal fluid of normal subjects or of patients with multiple sclerosis. We found no significant abnormalities in blood platelets, coagulation factors, serum platelet-like activity, or fibrinogen levels. Elevated cerebrospinal fluid protein and sedimentation rates were noted in several patients. An increased capillary fragility was frequently observed.

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Clinical Material

A total of 10 patients—9 men and 1 woman—were included in this study. The status of their disease ranged from recent onset with fairly rapid progression to a process which had lasted over 15 years and was slowly progressive at present. The severity of the disease process varied from slight impairment of ambulation to almost complete helplessness. The ages of the patients ranged from 32 to 48 years.

The patients were hospitalized as follows: one in the Medical College of Virginia Hospital, one in the Richmond City Home, and eight in the Division of Neurology at the McGuire Veterans Administration Hospital.

All of the patients manifested such clinical findings as nystagmus, ataxia, paresis, pyramidal tract signs, sensibility disturbances, and sphincter disorders. The present rate of progression of the disease process, its severity, and its duration are indicated in Table 1.

Clinical Summary of Cases

Case 1.—A white woman, aged 33. Four years previously she noted episodes of staggering gait, tremor, and burning sensations in her muscles. These cleared spontaneously without coming to the attention of a physician. Eight months ago she noted the onset of what has proved to be rapidly progressive ataxia in her legs and right arm and weakness in both legs. During this recent exacerbation she has experienced episodes of blurred vision and numbness in her hands and feet. She has had urinary frequency and incontinence, but no fecal incontinence. The patient is irritable

TABLE 1.—*Rate of Progression, Severity, and Duration of Multiple Sclerosis in Ten Patients*

Patient No.	Race *	Sex	Age	Present Rate of Progression	Severity	Duration of Disease, Yr.
1	W	F	33	Rapid	Mild	4
2	N	M	32	Rapid	Very severe	14
3	W	M	37	Very slow	Severe	9
4	N	M	42	Slow	Very severe	10
5	W	M	48	Rapid	Severe	4-5
6	W	M	48	Rapid	Severe	13-14
7	W	M	33	Rapid	Very severe	11-12
8	W	M	37	Rapid	Severe	9
9	W	M	45	Rapid	Very severe	14
10	W	M	34	Slow	Moderate	5

* W=white; N, Negro.

and emotionally unstable. Examination revealed marked loss of pain, touch, position, and vibration sensation in both legs, slight nystagmus on horizontal gaze, slight pallor of the optic disks, and a positive Babinski sign and hyperactive deep tendon reflexes in the right leg.

CASE 2.—A Negro man, aged 32. The disease process began 14 years ago with intention tremor of both arms, which was followed in time by progressively ataxic gait, diplopia, blurred vision, slurred speech, head nodding, weakness of trunk and leg muscles, numbness of the hands, and urinary incontinence. He has had a series of exacerbations and remissions, with an over-all steady progression of the disease. Currently, he is euphoric and restricted to a wheel chair. Recently there has been marked progression of symptoms. Examination revealed gross nystagmus, tremor, incoordination, and weakness. There was also bilateral optic atrophy, a bilateral Babinski sign, and absence of superficial abdominal reflexes.

CASE 3.—A white man, aged 37. Nine years ago he experienced a period of weakness and incoordination in his legs. After a two-year remission this difficulty occurred again, this time with additional gross intention tremor in his right arm and hand. For the past seven years his disease has undergone mild exacerbations and remissions, the over-all condition remaining fairly stationary. He gives a history of diplopia, blurred vision, and numbness of both legs and the right hand. He manifests urinary and fecal incontinence and euphoria and is confined mostly to a wheel chair. Examination revealed nystagmus at rest and on horizontal gaze, atrophy of the left optic disk, impaired pain, vibration, and position sensation, and a bilateral sustained ankle clonus and Babinski sign.

CASE 4.—A Negro man, aged 42. This patient is deaf, lethargic, dysarthric, and moderately demented as the result of long-standing, slowly progressive disease. Initial leg weakness was followed by gross intention tremor of both arms and bowel and bladder incontinence. He is now confined entirely to a wheel chair and is helpless. His physical findings include nystagmus at rest and on horizontal gaze, and bilateral optic atrophy, as well as severe paresis, clonus, and a positive Babinski sign in both legs. Proprioception and vibration sensations were impaired in both feet.

CASE 5.—A white man, aged 48. His disease began about five years ago with insidious onset of generalized weakness and ataxic gait, followed by the development of an area of hyperesthesia on his right arm. There has been steady progression of symptoms without remission. He has deteriorated rapidly in the past few months, presently being confined to a wheel chair and subject to diplopia, blurred vision, and fecal incontinence. He presents nystagmus on horizontal gaze, right internal strabismus, poor vision, bilateral optic atrophy, and marked muscle weakness. There is also impaired position and vibration sensation in both legs, a bilateral positive Babinski sign, hyperactive deep tendon reflexes, and absence of superficial abdominal reflexes.

CASE 6.—A white man, aged 48. At age 26 he had diplopia, of unknown etiology, for nine months. Eight years later he developed an ataxic gait, which slowly increased in severity for the following 10 years. The disease process suddenly became worse four years ago, and he soon developed diplopia, failing vision, slow slurred speech, progressive intention tremor and incoordination in both upper extremities, and fecal and urinary incontinence. He manifests marked nystagmus on horizontal gaze, atrophy of the right optic disk, intention tremor, incoordination, and marked leg weakness. In addition, there are a positive Babinski sign and sustained ankle clonus bilaterally, hyperactive deep tendon reflexes, and impaired position, vibration, and pain sensation.

CASE 7.—A white man, aged 33. With onset of intention tremor in both arms and ataxic gait about 12 years ago, his disease progressed slowly over the following seven years to include facial numbness and periodic blurring of vision. For the past

five years the progress has been rapid and steady, with a few brief remissions. He has been wheelchair-ridden for the past two years and has developed urinary incontinence, severe intention tremor in his arms, marked generalized muscle weakness, slow slurred speech, and euphoria. Examination revealed gross horizontal and vertical nystagmus, various ocular muscle palsies, atrophy of the right optic disk, and impaired position and vibration sensation in both legs. There were sustained ankle clonus and positive Babinski sign bilaterally, hyperactive deep tendon reflexes, and absence of superficial abdominal reflexes.

CASE 8.—A white man, aged 37. Leg weakness first occurred nine years ago. Two years later the disease process increased to include failing vision, progressive ataxia, greater weakness in his legs, and urinary incontinence. Confined to a wheel chair, he has recently developed intention tremor of both arms, fecal incontinence, and weakness and numbness in his left hand. He presents moderate horizontal nystagmus, atrophy of the right optic disk, generalized weakness, and marked sustained clonus in his ankles and knees. Hyperactive deep tendon reflexes, impaired vibration sensation, and a bilateral positive Babinski sign were also noted.

CASE 9.—A white man, aged 45. His first symptom was transient blindness and diplopia at age 31. Two years later he noted progressive leg weakness and ataxia, which finally confined him to a wheel chair, four years ago. His disease process has grown to include episodes of diplopia and blurred vision; slow slurred speech; weakness, intention tremor, and incoordination in his arms; burning sensations in his right arm and shoulder; marked leg weakness, and urinary incontinence. Examination revealed nystagmus on horizontal gaze, bilateral optic atrophy, various ocular muscle palsies, a bilateral positive Babinski sign, left ankle clonus, and impaired vibration sensation in both feet.

CASE 10.—A white man, aged 34. The disease began about five years ago with transient diplopia, followed by persistent blurred vision, progressively increasing right-leg weakness and ataxia, slow labored speech, and numbness of his right leg. His disease process includes fecal and urinary incontinence. He appears slightly deaf and mentally slow. There is nystagmus on horizontal gaze, early bilateral optic atrophy, intention tremor in his legs and left arm, and reduced position and vibration sensation. The Babinski sign was positive bilaterally, and there was left ankle clonus.

Laboratory Methods and Materials

Venous blood was obtained from patients by the two-syringe technique, using siliconized equipment. Amounts of blood were added to anticoagulants as required for each type of test, performed according to the methods used in this study. Simultaneously, control samples of blood were obtained from healthy volunteers, using the same method of collection as for the patients. All blood tests were performed during the day the samples were drawn.

Samples of spinal fluid were obtained by means of lumbar punctures, and tests were performed on the specimens within eight hours after collection. When necessary, samples of spinal fluid were frozen immediately, kept at −20 C, and thawed shortly before use. Tests involving cerebrospinal fluid were performed on nine of the patients, as no spinal tap could be done in Case 1.

Control samples of cerebrospinal fluid were obtained from three patients without primary neurological disorders. These samples were frozen immediately, kept at −20 C, and used throughout the study.

Blood platelets and changes in their function in progressive multiple sclerosis were evaluated by platelet count (Rees-Ecker method) and morphology, capillary fragility,[1] clot retraction,[2] and thromboplastin generation test.[3]

Blood vessels were investigated by means of bleeding time (Duke method) and capillary fragility determination.[1]

Other coagulation tests performed included the following: clotting time determination (Lee-White method); Quick's one-stage prothrombin concentration test,[4] and evaluations of Factor V ("accelerator" globulin),[5] Factor VII (convertin),[6] and fibrinogen[7,8] levels. Fibrinogen was determined by the micro-Kjeldahl method on 0.2 ml. of plasma clotted by the addition of 0.2 ml. of 0.025 M $CaCl_2$ in 5 ml. of saline and of one drop of Parke-Davis & Company's topical thrombin in a concentration of 1,000 units per milliliter.

Partial thromboplastin time[9] and serum platelet-like activity[10] (modified O'Brien method) were evaluated in each patient. In our study we used only the portion of the

TABLE 2.—*Blood and Spinal Fluid Findings in Ten Cases of Multiple Sclerosis*

Component	Normal Values	Patient 1	2	3	4	5	6	7	8	9	10
Hemoglobin	12-17 gm. %	13.5	15.8	16.0	14.0	16.4	17.0	16.0	16.0	15.8	15.6
Red blood cells	4.2-5.8 M per cu. mm.	4.20	4.85	5.03	6.00	5.38	5.37	5.46	4.72	5.44	5.08
White blood cells	5,000-10,000 per cu. mm.	8,650	5,350	6,400	6,600	11,150	9,800	7,650	7,900	8,100	6,150
Neutrophils	54%-62%	72	58	72	70	59	59	54	59	63	54
Lymphocytes	25%-33%	21	29	23	22	36	31	30	29	27	37
Monocytes	3%-7%	5	7	2	5	2	8	8	8	6	6
Eosinphils	1%-3%	2	6	3	2	3	0	8	2	4	2
Basophils	0-0.75%	0	1	0	1	0	2	0	1	0	1
Hematocrit	Men: 47±5 ml. %; women: 42±5 ml. %	40	43	48	47	45	49	47	48	46	47
Cap. frag. test	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.
Platelets	180,000-350,000 per cu. mm.	189	283	175	211	276	204	163	146	290	382
Bleeding time	1-3 min.	2.0	5.5	14.0	2.5	8.5	5.0	6.0	3.0	8.0	4.5
Clot retraction	Good in 60 min.	N	N	N	N	N	N	N	N	N	N
Thromb. gen. time	10 sec. after 6 min. of incubation	N	N	N	N	N	N	N	N	N	N
Description of platelet morphology	Normal	N	Many irreg. & in clumps	Some irreg. & in clumps	Some irreg. & in clumps	Large, irreg. & in clumps	Many irreg. & enlarged	Some irreg.	Some irreg., enlarged, & in clumps	Some irreg.	Some irreg., enlarged & in clumps
Clotting time	5-10 min.	8.0	8.0	7.5	10.0	9.0	9.5	10.0	8.5	10.0	9.0
Prothrombin concentration	50%-100%	60	50	75	60	60	75	60	50	100	100
Factor V level	80%-120%	92	85	100	90	84	92	88	85	100	100
Factor VII level	70%-120%	80	82	100	86	83	95	70	90	82	95
PTT	80-120 sec.	82	84	106	117	85	87	118	106	83	86
Fibrinogen level	200-400 mg. %	289	370	313	311	282	354	253	364	481	327
Sedimentation rate	Men: 0-9 mm/hr.; women: 0-20 mm/hr.	13	25	8	7	16	16	6	21	28	17
CSF cells	0-8 (L)	...	0	0	0	4 (L)	2 (L)	2 (L)	0	0	0
CSF protein	15-40 mg. %	...	42	20	10	58	80	350	58	52	24

* Cap. frag. test indicates capillary fragility test; CSF cells, total cell count and type in cerebrospinal fluid; CSF protein, total protein in cerebrospinal fluid; L, lymphocytes; PTT, partial thromboplastin time; Thromb. gen. time, thromboplastin generation time.

O'Brien method in which the clotting time of the mixture was determined without the determination of the thrombin generation time and the fibrinogen time.

Sedimentation rates [11] were determined in an effort to reevaluate reports in the literature of their being increased in multiple sclerosis.

Other hematologic studies performed include microhematocrit determination, red cell count, and white cell and differential cell counts. Cerebrospinal fluid was examined for cell count and total protein concentration.

The ability of spinal fluid of normal subjects and of multiple sclerotic patients to substitute for tissue thromboplastin was evaluated by the use of Quick's one-stage prothrombin-time test, in which the spinal fluid activity was compared with tissue thromboplastin (Difco) activity and with isotonic saline as controls.

The cerebrospinal fluid was evaluated for its blood thromboplastic activity in the following manner: A mixture of normal alumina plasma, serum, and platelets, as used in the thromboplastin generation test,[3] was used as a source of blood thromboplastin during the period of incubation of this mixture between four and eight minutes.

The addition of this mixture to normal and Factor-VII-deficient plasma showed no appreciable difference in clotting time (data to be published), as opposed to marked prolongation of the clotting time of Factor-VII-deficient plasma to which tissue thromboplastin was added. Our test for blood thromboplastic activity was performed by the substitution for blood thromboplastin of saline (as a control) and of the spinal fluids of normal subjects and of patients with multiple sclerosis, added to normal and Factor-VII-deficient citrated plasmas and recalcified. Both normal and Factor-VII-deficient plasma had been frozen at −20 C for approximately three weeks prior to use.

Results

The results of the tests presented in Table 2 reveal normal hemoglobin concentration, hematocrit reading, clotting time, and clot retraction. The red and white blood cell counts were all within normal ranges except in one case of each, and in neither of these instances was it elevated significantly.

There was no consistent significant abnormality of the white blood cell differential count. The neutrophils were slightly elevated in four cases, and the lymphocytes were somewhat low in three cases and high in two instances. There was a very slight monocytosis in three cases and a moderate eosinophilia in three cases.

The capillary fragility test was positive in 8 of the 10 cases. The two negative tests were read in Negroes, in whom petechiae are difficult to observe because of the dark skin.

The bleeding time was prolonged in 7 of the 10 patients, ranging from 1½ to 10 minutes above normal. The average bleeding time for our patients was six minutes.

The platelet count was normal in six of the patients, slightly low in three, and slightly elevated in one. In the evaluation of platelet morphology in the peripheral blood smear, some platelets were found to be abnormal, being enlarged and/or irregular in nine of the patients. In spite of the slight variation in platelet counts and the abnormalities in platelet morphology, the thromboplastin-generation test using these platelets was normal in all cases.

Of the eight patients with a positive capillary fragility test, four had normal platelet counts, three had slightly low counts, and one had a high count.

The capillary fragility test was positive in seven of the patients who exhibited some abnormal platelet morphology and in one subject with normal platelets. It was negative in the two Negroes in our series, both of whom had some abnormal platelet morphology.

TABLE 3.—*Prothrombin Concentration and Factor V and Factor VII Levels*

Prothrombin Concentration, % of Normal				
	Range of Normal Values			
Concentration, %	50	60	75	100
No. of cases	2	4	2	2

Factor V and Factor VII Levels, % of Normal					
	Normal Range				
Concentration, %	70-79	80-90	91-100	101-110	111-120
Factor V, no. of cases	0	5	5	0	0
Factor VII, no. of cases	1	6	3	0	0

The prothrombin concentration was found to be within the range of normal in all patients, but in only two was the prothrombin concentration 100%. In six of the remaining eight cases the prothrombin level was at or near the low level of normal.

Likewise, the levels of Factor V and Factor VII were found to be within the normal range in all patients; but they, too, tended to fall in the lower ranges of normal.

These findings are shown in Table 3. The results of the partial thromboplastin time test are within the normal range.

Determination of the fibrinogen level found it normal in nine of these tests and moderately elevated in one. The one elevated level was in a patient with a disease process graded as very severe, rapidly progressive.

The sedimentation rate was elevated in six cases.

The cell count of the cerebrospinal fluid was normal in all nine of the patients, but the total protein was elevated in six cases.

Each group of figures in Table 4 and each group of figures in Columns 3, 4, and 5 of Table 5 represent the results of 18 tests. Those performed on spinal fluid samples obtained from nine patients with multiple sclerosis represent duplicate tests.

The mean values were evaluated, and the standard error of the mean and the standard deviation were utilized in arriving at the statistical significance of the differences observed.

Clotting time of the tests in Table 4 utilizing normal plasma were not significantly different from those using plasma of patients with multiple sclerosis.

The clotting times of the spinal fluid of normal subjects or of patients with multiple sclerosis in mixtures including tissue thromboplastin did not differ significantly from those of the mixtures with saline used instead of spinal fluid.

When tissue thromboplastin was omitted from the test mixtures, the clotting times of the test mixtures using normal spinal fluid or the spinal fluid of patients with multiple sclerosis did not differ significantly from one another or from those of the

TABLE 4.—*Evaluation of Cerebrospinal Fluid for Tissue Thromboplastic Activity* *

	Tests Incorporating Tissue Thromboplastin			
	Tissue Thromboplastin	Tissue Thromboplastin + Saline	Tissue Thromboplastin + Normal Spinal Fluid	Tissue Thromboplastin + Patient's Spinal Fluid
Normal plasma	11.4±0.3; 0.9	12.4±0.3; 0.9	12.2±0.3; 0.9	12.1±0.2; 0.7
Patient's plasma	11.6±0.2; 0.7	12.4±0.2; 0.5	12.5±0.3; 0.8	12.1±0.4; 1.1

	Tests Without Tissue Thromboplastin		
	Saline (0.2 Ml.)	Normal Spinal Fluid + Saline	Patient's Spinal Fluid + Saline
Normal plasma	61.8±1.2; 3.5	65.8±3.6; 10.9	69.7±4.8; 13.7
Patient's plasma	65.2±2.5; 7.5	70.8±2.7; 8.2	68.8±3.0; 8.8

* Numbers represent clotting times, in seconds. Each group of three figures represents (from left to right) the mean value of all the tests, the standard error of the mean, and the standard deviation. The volume of each component used is 0.1 ml. unless otherwise stated. Each of the test mixtures was recalcified by the addition of 0.1 ml. of a 0.025 M solution of calcium chloride.

TABLE 5.—*Evaluation of Cerebrospinal Fluid for Blood Thromboplastic Activity* *

	Tissue Thromboplastin	Blood Thromboplastin	Controls	Tests	
			Saline	Normal Spinal Fluid	Patient's Spinal Fluid
Normal plasma	13.5	13.2	69.8±3.3; 10.0	73.8±2.1; 6.4	69.1±3.4; 10.2
Factor-VII-deficient plasma	37.0	12.4	61.7±3.6; 10.8	67.0±3.1; 9.4	64.9±3.0; 9.0

* Numbers represent clotting time, in seconds. The numbers in the first two columns represent averages of a series of tests done by one of us in a previous study. Each group of figures appearing in Columns 3, 4, and 5 represents (in each box, from left to right) the mean value of all the tests, the standard error of the mean, and the standard deviation. The volume of each component used is 0.1 ml. Each of the test mixtures was recalcified by the addition of 0.1 ml. of a 0.025 M solution of calcium chloride.

control mixtures using saline. This indicates that neither normal spinal fluid nor the spinal fluid of multiple sclerosis patients has any tissue-thromboplastic activity.

Table 5 shows that the addition of blood thromboplastin to Factor-VII-deficient plasma or to normal plasma gives similar coagulation times. When tissue thromboplastin is used, the clotting time of Factor-VII-deficient plasma is markedly longer than that of normal plasma.

When the spinal fluid of normal persons or of multiple sclerosis patients is added to normal or to Factor-VII-deficient plasma, the clotting times obtained do not differ significantly from one another or from those of the control mixtures with saline used instead of spinal fluid.

TABLE 6.—*Serum Platelet-like Activity of Normal and Multiple Sclerosis Patients' Sera* *

	Normal	Patients
Platelet-rich plasma (0.3 ml.) + Saline (0.2 ml.)	96.3±5.6; 16.7	92.1±4.9; 14.8
Platelet-rich plasma (0.3 ml.) + Serum (0.2 ml.)	79.9±4.1; 12.2	79.8±4.4; 13.3
Platelet-poor plasma (0.3 ml.) + Saline (0.2 ml.)	136.2±5.4; 16.2	134.6±5.8; 17.4
Platelet-poor plasma (0.3 ml.) + Serum (0.2 ml.)	83.3±3.3; 9.9	85.6±3.4; 10.1

* Numbers represent clotting times, in seconds. Each group of figures represents (from left to right) the mean value of all the tests, the standard error of the mean, and the standard deviation. In each instance 0.3 ml. of plasma and 0.2 ml. of either serum or saline were recalcified with 0.3 ml. of 0.025 M solution of calcium chloride.

This indicates that neither the spinal fluid of normal subjects nor that of multiple sclerosis patients has any blood thromboplastic activity.

Each group of figures in Table 6 represents the results of duplicate tests performed on blood samples obtained from 10 patients with multiple sclerosis or from 10 healthy volunteers.

Serum platelet-like activity is considered to be normal when the addition of serum to platelet-poor plasma results in a clotting time approaching that of a mixture of platelet-rich plasma and saline.

Figures presented in Table 6 show such normal results when the components of either normal blood or that from multiple sclerosis patients are examined. It can be seen that there is no significant difference between the serum platelet-like activity of normal subjects and that of patients with multiple sclerosis.

Comment

Our study was prompted by the fact that various investigators have reported abnormalities in the plasma and formed elements of the blood in multiple sclerosis. Theories have been advanced that there is "sludging," [12] or increased coagulability [13] of blood which causes venular thromboses in the central nervous system.

In his observation of blood in bulbar conjunctival vessels of patients with multiple sclerosis, Roizin [12] noted a high incidence of "sludging" of this blood and postulated that "sludged" blood might be considered as one of the pathogenic factors

underlying the fleeting symptoms or the insidious relapses observed in multiple sclerosis. He also felt that thrombosis of blood vessels in multiple sclerosis might be due to lumps of "sludge" in the blood which were caught in the small blood vessels and might thereby occlude them, either partially or completely. Putnam [13] stated that the list of exogenous factors which tend to increase the coagulability of the blood corresponds closely with the list of exogenous factors which appear to precipitate the onset or exacerbations of multiple sclerosis. He reported that patients with a remittent form of the disease who were treated with doses of bishydroxycoumarin (Dicumarol) sufficient to raise the prothrombin time to 30 seconds continuously had no fresh symptoms or obvious acute exacerbations.

As a result of his studies [14-17] in 1935, 1937, and 1939, Putnam felt that vascular occlusion is primary to the histologic changes and the formation of sclerotic plaques in the central nervous system in multiple sclerosis. He was of the opinion [15] that the basic abnormality lies in the clotting mechanisms of the blood. He found [16] that small plaques tend to surround engorged veins, and when a thrombus occurs in a vein, an area of fresh degeneration appears close to it. Putnam [15] noted that thrombi are occasionally found in organs other than the central nervous system in multiple sclerosis.

Macchi [18] reports evidence that, in addition to the primary process of demyelination, there is vascular participation in the pathogenesis of multiple sclerosis; plaques are arranged around congested venules, which further facilitate demyelination.

Persson [19] feels that generalized "sludging" of blood cannot explain the confinement of venular thromboses and associated plaques to the central nervous system. He has found a platelet-agglutinating substance in the cerebrospinal fluid in multiple sclerosis,[19,20] this substance also being present in cerebrospinal syphilis, but not being found in other neurological diseases, such as hemiplegia, Huntington's chorea, and cerebral arteriosclerosis. The number of adhesive platelets increases in the prodromal stage of thrombosis; and then, with the actual formation of thrombi, there is a sudden drop in the number of platelets in the blood, especially in the number of adhesive platelets.[21]

That there are connections between the perivascular channels of the brain and the subarachnoid space was demonstrated by Weed,[22,23] who also stated that in abnormal conditions cerebrospinal fluid may on occasion reverse its flow.

Persson [19] postulates that passage of cerebrospinal fluid in multiple sclerosis into the cerebral capillaries, and thence into the small veins in the central nervous system, causes the formation of thrombi of agglutinated platelets; he expressed the opinion that even though these thrombi may not be associated with plaques and lesions of multiple sclerosis, the plaques do occur as a result of thrombosis in the small veins of the central nervous system.

A study by Kittleson [24] indicates that there is no correlation between the degree of platelet agglutination and the presence of multiple sclerosis and postulates that the platelet agglutination observed by Persson [19,20] may be due to recalcification of the platelet suspension by the cerebrospinal fluid. Feldman [25] also was unable to confirm the presence of the thrombocyte-agglutinating substance reported by Persson.

Savitsky [26] reports an abnormally rapid clot retraction time in cases of active or fluctuating multiple sclerosis. He does not, however, give support to the theory of a thromboembolic etiology of the disease and feels that there is no indication that pathological changes in the blood-clotting mechanisms cause multiple sclerosis.

Fog [27] has observed that the number of platelets in the peripheral blood show greater variations in patients with multiple sclerosis than in normal people and that these fluctuations are greatest when the disease is active. The platelet count is lowest during the active stage of the disease and increases during remissions.

Because the reported changes in the function of the cerebrospinal fluid may be correlated with the presence of abnormal components in the spinal fluid and blood plasma, we surveyed the literature and found reports of increase of γ-globulin concentration in the cerebrospinal fluid in this disease.[28,29] The serum protein changes reported in multiple sclerosis include a decrease in the albumin with an increase in the α_2-, β-, and γ-globulin levels,[29] a decrease in the albumin with an increase in the γ-globulins, but normal levels of α_2- and β-globulins[28,30] and a decrease in the albumin and total protein levels.[31] These changes in the serum in multiple sclerosis may be related to changes in liver function tests found by Dobin.[32] Persson's study[33] of liver function in multiple sclerosis indicates that there is no serious liver damage.

Serum protein changes[29] do not differ from those found in other neurological diseases; however, the levels of total protein and γ-globulins in the cerebrospinal fluid were increased in multiple sclerosis.

Cullen[34] believes that after meals high in fat content certain changes occur in the blood consisting of an increased adhesiveness and aggregation of the red blood cells, and sometimes clumping of platelets. These phenomena are accompanied by slowing, and even at times complete cessation, of flow of the blood. He feels that while dietary fat intake is not the basic cause of multiple sclerosis, a high-fat diet is an important and common precipitating or accelerating factor in persons susceptible to multiple sclerosis and may be an important factor in the pathogenesis of multiple sclerosis, as well as vascular thrombosis.

In his study of serum lipids in multiple sclerosis Gerstl[35] found that only the levels of dienoic acid were elevated significantly in the patients whom he classified as "inactive"; he noted normal levels of dienoic acid in his patients with "active" multiple sclerosis.

Persson[36] reports a consistent elevation of the total lipids in the serum of men with multiple sclerosis, this rise being independent of the stage of activity of the disease; a similar rise in serum total lipids was seen in certain female patients with multiple sclerosis.

That the hemoglobins levels, red and white cell counts, microhematocrit values, and white cell differential counts of the patients in our series show no significant abnormalities corresponds with the findings of Dekaban.[37]

The facts that 8 of our 10 patients had positive capillary fragility tests and that 7 had prolonged bleeding times suggest that patients with multiple sclerosis may have some abnormality of their vascular system. This is in contrast to the findings of Dekaban,[37] who reported that the Rumpel-Leede capillary fragility tests and the bleeding times were usually within normal limits in the patients he examined.

The evaluation of the blood platelets showed the counts to be normal in most cases, the morphology of some platelets to be abnormal in 9 of 10 blood smears, the clot retractions to be good, and the thromboplastin generation tests to be normal in all cases.

The normal platelet counts and the abnormal platelet morphology, together with the defect in the vascular system, may suggest a possible thrombasthenia, which by poor platelet function might give rise to the defect in the vascular system. However, the normal platelet function reflected in the clot retraction and thromboplastin generation tests tends to question the existence of a thrombasthenic state. Thus, the defect in the vascular system seen in these multiple sclerosis patients may be due to some factor other than blood platelets.

One cannot eliminate the possibility of a generalized vascular deficiency which may cause circulatory and thrombotic tendencies limited to the central nervous system because of the differences in the vascular bed and the consistency of tissues surrounding the blood vessels in the brain and spinal cord as compared with those in other parts of the body.

The determinations of prothrombin concentration and Factor V and Factor VII levels were found to be within the normal range. As shown in Table 3, the prothrombin concentration and the Factor V and Factor VII levels tend to fall in the lower ranges of normal. These results question the theory of generalized increased coagulability of the blood in multiple sclerosis, proposed by Putnam.[13] Our findings support the report of Feldman[25] of normal to slightly decreased blood coagulability.

Although 9 of our 10 patients were judged clinically to have an active progression of their disease process, the fibrinogen levels of 9 were normal and that of 1 moderately elevated. There appears to be no correlation between the fibrinogen level in each patient and the severity or the rate of progression of the disease. Thus, we were unable to confirm the report of Persson[38] of a rise in the plasma fibrinogen level with the progression of multiple sclerosis.

The elevation of sedimentation rates observed in 6 or our 10 patients corresponds closely to that reported by Dekaban.[37] The increased sedimentation rates may be due to certain of the complications of long-standing cases of multiple sclerosis, such as chronic urinary infections and infected decubitus ulcers, rather than to the basic process of multiple sclerosis.

Experiments performed on the cerebrospinal fluid revealed that neither normal spinal fluid nor the spinal fluid of multiple sclerosis patients possesses any tissue- or blood-thromboplastic activity.

As frozen normal spinal fluid and fresh spinal fluid of multiple sclerosis patients were used in the tests of these for blood thromboplastic activity, it was also shown that freezing does not cause any activation of either tissue or blood thromboplastin in normal spinal fluid.

The evaluation of serum platelet-like activity revealed that the serum of multiple sclerosis patients has the same ability to substitute for platelets as does the serum of a normal person.

Summary and Conclusions

Ten patients with clinically well-established diagnoses of multiple sclerosis were examined for possible changes in blood platelets and coagulation factors and for blood and tissue thromboplastic activity in the cerebrospinal fluid. In nine of these patients there was recent progression of symptoms, and in eight the degree of physical disability was considered to be severe.

We have arrived at certain conclusions as a result of this study.

1. Neither normal spinal fluid nor the spinal fluid of multiple sclerosis patients has any tissue or blood thromboplastic activity.

2. Freezing normal spinal fluid does not cause the appearance of tissue or blood thromboplastic activity in it.

3. There is normal to slightly decreased coagulability of blood in multiple sclerosis as determined by prothrombin concentration, Factor V and Factor VII levels, and clotting time.

4. People with multiple sclerosis may have some defect in their vascular system which tends toward an increased capillary fragility and prolonged bleeding time. This defect is not due to low platelet levels or to poor platelet function.

5. The serum of patients with multiple sclerosis has normal platelet-like activity.

6. The plasma fibrinogen levels are usually normal in cases of multiple sclerosis with recent progression of symptoms.

7. There is no significant abnormality in multiple sclerosis with respect to hemoglobin level, red and white blood cell counts, white cell differential count, and hematocrit.

8. The sedimentation rates are often elevated in multiple sclerosis.

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The opinions expressed in this paper are those of the authors and are not necessarily those of the Veterans Administration.

Department of Clinical Pathology, Medical College of Virginia (Dr. Kupfer).

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Society Transactions

LOS ANGELES SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Jan. 15, 1958

A Brief History of Modern Brain Maps and Models. Dr. Richard D. Walter.

Various types of diagrams, maps, and models of central nervous system activity have been constructed since man first became aware of the brain and mentation. Particular attention, however, will be given to the postphrenological period, leading up to the present time. These models can be epitomized by the changing concept of the "integrator"—its anatomical location and its function. The "center of ideation" and other subcenters with specialized but limited functions usually are represented by circles with vague anatomical outlines. An early example of this is Charcot's diagram for the interrelations of the "center of ideation," the "center of auditory perception," and the "center for motor control." The concepts of Head, Holmes, and Prince, involving the thalamic and cortical connections, present a more anatomical, but somewhat less functional, model. More modern diagrams and models become more complex with the introduction of the reticular system, nonspecific thalamic circuits, and the structures within the rhinencephalon. The "integrator" in many diagrams must assume the function of a homunculus—a little brain within the brain that performs correlations, abstraction, and the initiation of voluntary action, as well as integration. Black diagrams of the central nervous system nearly always include such an integrator—usually with an implied electronic analogy. However, the models based on present neurophysiology indicate a less definite anatomical location for the "center" and a greater likelihood of these functions being performed by complex interconnections between more discrete systems.

The Phylogeny of Spatial Perception. Dr. Robert D. Tschirgi.

Capacity to distinguish stimulus position is measured by the ability of an organism to respond differently to the same stimulus modality when that stimulus is applied to different spatial loci within the sensorium. It is hypothesized that this capacity has evolved in the animal kingdom by progressive increase in asymmetry of the nervous system, which is associated with, but is not necessarily the same as, over-all body symmetry. Thus, the amount of spatial information conveyed by a stimulus increase with increasing asymmetry of neural organization, and the following series of "Euclidian" organisms is presented to illustrate this principle. Each organism consists of 128 stimulable sites, but these are arranged in increasingly asymmetrical patterns. Spatial information (I), which is transmitted through the organism by a stimulus, is defined as a logarithmic function of the ratio of two probabilities: The numerator is the probability of the occurrence of a particular response after application of the stimulus, and the denominator is the probability of the occurrence of the response before the stimulus is applied. In all cases the stimlus remains the same except for the site of application.

$$I=\log_2 \frac{p(\text{a posteriori})}{p(\text{a priori})}$$

1. *Spherically Symmetrical Organism.*—Response to stimulus is identical, relative to stimulus site, for all sites of application.

$$I_s=\log_2 \frac{1/1}{1/1}=0$$

2. *Radially Symmetrical Organism.*—Response to stimulus is identical, relative to stimulus site, for all sites of application on any given circumference, but varies with each stimulable point along the asymmetrical (anterior-posterior) direction.

$$I_r=\log_2 \frac{1/1}{1/x}=>I_s,<6$$

where $x>1$ and <64, depending upon the number of stimulable points in each circumference; i. e., for an organism with 16 circumferential bands, each containing 8 stimulable points $x=16$ and $I_r=4$.

3. *Bilaterally Symmetrical Organism.*—Response to stimulus is identical, relative to stimulus site, for homologous (right-left) sites of application, but varies with each stimulable point along asymmetrical (anterior-posterior and dorsal-ventral) directions.

$$I_b=\log_2 \frac{1/1}{1/64}=6$$

4. *Asymmetrical Organism.*—Response to stimulus varies for every stimulable site.

$$I_a=\log_2 \frac{1/1}{1/128}=7$$

Man approaches the asymmetrical organism insofar as the two halves of his nervous system are functionally dissimilar.

Regular Meeting, Feb. 10, 1958

Hepatolenticular Degeneration (Wilson's Disease). Dr. D. Denny-Brown, Boston.

The clinical signs of Wilson's disease in a large group of personally observed cases were reviewed, with particular reference to the prominence of different forms of dystonia in the younger age groups and the emergence of hepatotoxic types of tremor in the older age groups. It was concluded that the differences between the neurological symptomatology of Wilson's disease and that of intoxication by metals, such as mercury and manganese, could probably be accounted for by duration and type of exposure, rather than by specific effect of the copper ion. Cases of characteristic symptomatology without disorder of copper metabolism were cited. Wilson's disease was viewed as a specific type of a more general syndrome with varied causation. In Wilson's disease the amino-aciduria and cupuria indicate a fundamental defect. The technique of demonstration of copper by rubeanic-acid staining of the liver biopsy specimen by the Uzman method was reviewed, and the significance of chelated copper in liver, glia, and cornea was discussed. No proved case of Wilson's disease with neurological signs had been seen without a demonstrable Kayser-Fleischer ring. The interrelation of corneal deposit and chelating properties of proteins was discussed.

The results of treatment of Wilson's disease by dimercaprol U. S. P. (BAL) in 16 patients for periods up to eight years are presented. The most satisfactory results were in the cases with onset of neurological symptoms between the ages of 14 and 26. Of eight such patients, three whose symptoms had commenced at age 29 to 35, and had been present 7 to 13 years before commencing treatment, showed an excellent response for periods of 2 to 6 years and then succumbed to recurrent ascites. Of patients with age of onset between 7 and 15 years, one-half continued a moderate degree of improvement with dimercaprol therapy, the remaining four relapsing after intervals of 6 to 18 months, one with severe and fatal hepatitis, the acute onset of which occurred three months after the last dimercaprol treatment. The other three developed repeated bouts of myoclonus and myoclonic convulsions that had been resistant to any form of chelating treatment and present a new, and so far unsolved, problem.

Discussion

Dr. W. H. Oldendorf: We have recently had a well-established case of Wilson's disease at the Veterans Administration Center. He was treated with Penicillamine, 1.5 gm., daily for a period of four weeks. This was discontinued because he developed a personality change with marked hyperirritability and progressive confusion for several hours after awakening in the morning. This cleared immediately after cessation of the drug. After two weeks he was started on 1 gm. a day and within a day was again noted to be hyperirritable.

Regular Meeting, March 19, 1958

Visual Responses to Cortical Stimulation in the Blind. Dr. Tracy J. Putnam.

As far as we are aware, no previous attempts have been made to evoke visual impressions in the blind by stimulation of the occipital cortex. Two patients were referred by Dr. John Button, of East Orange, N. J., for this purpose.

Case 1.—Miss B., aged 36, had been blind since a decompressive operation for an obscure illness, at age 18, was carried out. Shortly afterward she developed a complete optic atrophy. She had no visual preception.

At operation, on Oct. 29, 1957, under local anesthesia, fine insulated wires were inserted into both occipital lobes through small drill holes, in a predetermined pattern and at a depth to end in the visual cortex. When a stimulating current, consisting of spike impulses of a peak value of 25 volts, at 8 to 75 per second, was applied, the patient reported that she "saw" flashes of light projected to the contralateral side.

The wires were left in place and were later connected to a similar stimulating apparatus, the output of which passed through a cadmium photocell. She learned to point this cell at a source of light and eventually to find her way around a room with its aid.

Case 2.—Miss A., aged 32, had been blind since the age of 5 years as a result of a severe head injury. She had a complete optic atrophy. An operation similar to that in Case 1 was carried out on Dec. 27, 1957. The impression of light was much less definite than in the first case and was accompanied by some discomfort. On the whole, the results were not sufficiently definite to justify further experimentation, and the wires were withdrawn two weeks later.

Regular Meeting, Sept. 17, 1958

Recent Developments in Memory and Amnesia. Dr. J. M. Nielsen.

It has recently become clear that the two classical types of memory, (1) memory of life experiences and (2) memory of intellectually learned facts, have different circuits in the brain. Memory of life experiences has a circuit through the hippocampus, and the proof is given by cases of bilateral removal of this structure (Scoville's operations, cases of Terzian and Ore and of Glees and Griffith, and a few cases of temporal lobectomy for epilepsy). Memory of intellectually learned facts is not affected by such removal but is affected

by lesions of the cortex. This is why patients with epileptic automatism (with hippocampal lesions) cannot form memory of life experiences during an episode, but they can utilize speech and knowledge of directions, etc. Also, patients with aphasia from cortical lesions are still oriented and have preserved intellect. It has been shown that a few persons utilize only one hippocampus for memories, and that in such persons a unilateral removal causes dementia.

Regular Meeting, Oct. 15, 1958

Polymyositis and Dermatomyositis. Dr. Carl M. Pearson.

Polymyositis and dermatomyositis are clinical variants of a similar pathologic disorder of the striated musculature. The cardinal symptom of both is muscular weakness, especially involving the proximal limb girdle, neck, and pharyngeal muscles. These disorders are not rare, as 19 cases of myositis have been seen at the University of California Medical Center within the past two and one-half years. In addition to dermatologic signs, which were prominent in dermatomyositis and minimal, atypical, or absent in polymyositis, nearly one-half the cases had rheumatic symptoms, oftentimes closely resembling rheumatoid arthritis. Three cases had an associated visceral malignancy.

An analysis of 27 initial clinical diagnoses made in these 19 cases revealed that 13 times the condition was considered to be a neuromuscular disease but that only in 3 instances was myositis considered to be likely. Diagnoses of muscular dystrophy, polyneuritis, or myasthenia gravis were also made several times initially. Ten initial diagnoses were made of rheumatic conditions, usually rheumatoid arthritis or systemic lupus erythematosus. Interesting laboratory features included an elevated serum transaminase, an abnormal serum protein electrophoretic pattern, and a positive latex-fixation test (for rheumatoid arthritis) in many cases. An abnormal electromyographic pattern was noted in all cases examined. Muscle biopsy tissue was obtained in all 19 cases, and the detailed histopathology was described.

Many cases, especially those with acute myositis and without accompanying malignancy, have responded favorably to adrenal steroid medication, which must be continued for long periods in most instances.

A Review of Some Current Concepts of Myelin. Dr. Frederick Wolfgram, and Dr. Augustus S. Rose.

Electron microscopy has provided a wealth of detail on the ultrastructure of myelin and on its formation. In particular, the question of whether peripheral-nerve myelin is formed from the axon or from the Schwann cell has been decided. Peripheral myelin is now regarded as an extension of the Schwann cell membrane, and is presumably formed by a wrapping of the Schwann cell around the axon. In the central nervous system it is not yet clear whether the oligodendrocyte plays a role analogous to that of the Schwann cell. Recently both peripheral and central nerve myelin has been successfully cultured in vitro. Advances in neurochemistry have documented a distinct difference in peripheral and central myelin in that the "proteolipids" are present only in the latter. These proteolipids have the unique property of being soluble in a mixture of chloroform and methanol. The role of the proteolipids in experimental allergic encephalomyelitis has been examined, and at least one of them has antigenic activity. However, at best, the proteolipids account for only a fraction of the total antigen. The recent discovery of some enzymes in myelin is of considerable importance in that it demonstrates that myelin proteins have functions other than a purely structural one.

Regular Meeting, Nov. 19, 1958

The "Tuning" of the Autonomic Nervous System and Some of Its Clinical Implications. Dr. Ernst Gellhorn.

Experiments are reported in which the central autonomic balance was altered by intrahypothalamic lesions or by injection of minute qualities of drugs into the anterior or the posterior division of the hypothalamus. Lesions in the posterior hypothalamus or injection of thiopental (Pentothal) in this area was accompanied by a loss of sympathetic tone (fall in blood pressure and heart rate) and a diminished reactivity of the sympathetic system. Lesions in the anterior hypothalamus or injection of thiopental in this area caused a slight increase in blood pressure and heart rate and an increase in sympathetic reactivity. The parasympathetic reactivity was reciprocally altered in both groups of experiments.

The central autonomic reactivity may be altered also through reflexes. The lowering of the blood pressure through drugs causing hypotension (acetylcholine, methacholine, histamine) increases sympathetic reactivity, whereas the rise of the blood pressure through norepinephrine diminishes it. Parasympathetic reactivity is altered reciprocally. Finally, it is shown that diminution of proprioceptive impulses through curare lowers hypothalamic sympathetic reactivity and hypothalamic-cortical discharges. The clinical implications are discussed.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION ON NEUROLOGY AND PSYCHIATRY

Harold R. Merwarth, M.D., President, New York Neurological Society, Presiding

Joint Meeting, Feb. 10, 1959

Cerebral Embolism: Clinical Course, Prognostic Signs, and Effects of Anticoagulation Therapy. DR. CHARLES E. WELLS.

The clinical courses of 97 episodes of cerebral embolism occurring in 82 patients have been analyzed. Sixty-three episodes occurred in patients who were not given anticoagulants, and 34 episodes occurred in patients who were treated with anticoagulants.

In the untreated groups 70% of the patients had rheumatic heart disease and 17% had arteriosclerotic or hypertensive cardiovascular disease. Forty-seven per cent were found to be in normal sinus rhythm when examined after the onset of the embolic phenomena. The onset was most frequent in the morning hours. Headache was a feature of onset in 25%, and in half of these it was of high intensity. Seizures occurred at the onset in 12.5%. The laboratory findings were nonspecific. Twenty-five of the episodes ended in death, and 35% resulted in severe permanent neurologic dysfunction.

A further study was made to determine what factors allow prediction of a good or a poor result soon after the onset of the cerebral embolism. The occurrence of seizures, prolonged coma, Cheyne-Stokes respirations, or a significant increase in signs or symptoms after onset was unlikely to be associated with good recovery. When paresis did not begin to diminish within 48 hours after onset, the chance for good functional recovery was slight.

A comparison was made between results in the 63 episodes in which anticoagulants were not given and in the 34 episodes treated with anticoagulants. In the untreated group 25% ended in death, whereas in the treated group 6% ended in death. Furthermore, in the untreated group, there were good results in 40% of patients, whereas in the treated group there were good results in 56% of patients.

Discussion

DR. HAROLD G. WOLFF: Dr. Wells has brought into focus the observation that in the patients who had no treatment 25% of the cerebral accidents ended in death and 35% resulted in serious deficits. In the group that had anticoagulant treatment only 6% died. It is of importance to know that when the anticoagulants are used properly their use does not seem to be associated with any worsening of the sequelae of the embolic accident. Also worthy of mention are some of the prognostic features. Apparently patients who exhibit, as sequelae of the accident, seizures, loss of consciousness, Cheyne-Stokes respirations, and progression of symptoms, and who show no improvement after 48 hours can be expected to do badly, whereas for those who begin to recover their strength in a relatively short time, especially if there has been no loss of consciousness, the prognosis is better.

Finally, it is impossible to overemphasize the importance of anticoagulant therapy being given by persons who are fully competent. Also, as those from the Bellevue Hospital study will point out after me, only a few people who have had vascular accidents are in a position to have this treatment. There is indeed considerable importance in selecting the right patient for anticoagulation therapy. Many of these patients have a very much damaged brain, and it is dangerous to leave them with these drugs. Since all of Dr. Wells' inferences rest on having selected comparable cases, I wish he would emphasize just how he chose the cases so as to make them comparable in his study.

DR. FLETCHER H. MCDOWELL: At the moment, cerebral embolism is the only variety of cerebral vascular accident whose course is clearly altered by anticoagulation therapy. We have found, as Dr. Wells mentioned, that the greatest difficulty is in selecting the right patients for anticoagulation therapy after a diagnosis of cerebral emboli or thrombosis. Only about one-third of 400 patients with cerebral vacular accidents at Bellevue were considered suitable for anticoagulation therapy. Many of them are sent to other institutions where facilities are inadequate for control of anticoagulation. Many of them are at an intellectual level which does not enable them to understand the use of these dangerous drugs. Other patients are so impaired that it is useless to try these drugs. This leaves us with one-third of our original group of patients suitable for treatment. This automatically means to me that anticoagulants are not an adequate answer for treatment of vascular diseases of the brain.

DR. CHARLES E. WELLS: In reply to Dr. Wolff's question: The two groups came from a series of patients admitted over a number of years. In going over all the prognostic signs, we found that both the treated and the untreated group had approximately the same percentage of poor prognostic

signs; so the two had episodes of similar severity before treatment was begun.

DR. HAROLD G. WOLFF: Are we right in assuming from what you said that the proportion of patients who died in episodes after anticoagulation treatment was 6%, as compared with 25% in the nontreated group?

DR. CHARLES E. WELLS: Yes.

DR. HAROLD G. WOLFF: So that the mortality was actually reduced to one-quarter of that of the untreated patients?

DR. HAROLD G. WELLS: That is correct.

Functional Relationships Between the Fastigial Nucleus and the Labyrinth. DR. MALCOLM B. CARPENTER.

Prior studies have indicated that isolated lesions of the fastigial nuclei and labyrinthectomy in the cat produce similar, but not identical, physiologic disturbances. Lesions confined to either the labyrinth or these nuclei produce profound disturbances of equilibrium and coordination. Disturbances resulting from these various lesions each undergo a relatively rapid attenuation, but do not entirely disappear.

Bilateral destruction of the fastigial nuclei in previously labyrinthectomized cats eliminates all compensatory adaptation which has occurred and appears to produce a summation of the deficits characteristic of the individual lesions. No significant attenuation of these summated disturbances occurs with time. The final result is the same when these lesions are inflicted in reverse sequence. These data have been interpreted as indicating that (1) the integrity of the labyrinth plays an essential role in the mechanism of accommodation to fastigial deficits; (2) the fastigial nuclei are essential for accommodation to bilateral labyrinthectomy, and (3) both the fastigial nuclei and the labyrinth make functional contributions to the maintenance of equilibrium and coordination of activity.

Discussion

DR. WALTER S. ROOT: The deficiency phenomena (loss of equilibrium, ataxia, etc.) seen after labyrinthectomy or lesions of the fastigial nuclei in the cat disappear or become less noticeable with time. The site of this compensation is generally thought to be the vestibular nuclei. Actually, the situation is more complicated, for Dr. Carpenter's results indicate clearly that when both labyrinths and fastigial nuclei are destroyed no compensation takes place. This must mean that compensation to either labyrinthectomy or injury of the fastigial nuclei occurs somewhere in the labyrinthine-vestibular nuclei-fastigial nuclei complex.

DR. HAROLD G. WOLFF: I wonder whether Dr. Carpenter will tell us, since these labyrinthine nuclei and fastigial nuclei have so many things in common, why we have these two systems. Why would not one do?

DR. MALCOLM B. CARPENTER: In response to Dr. Wolff's question as to why these two systems exist (fastigial and vestibular), I would say that these nuclei probably represent similar components of essentially the same system. Although the function of these different components is similar, certain basic differences are also present.

Subdural Hematoma: Pathogenesis of the Delayed Symptomatology. DR. E. JEFFERSON BROWDER and DR. HARRY A. KAPLAN.

The pathology of subdural hematoma and the clinical state associated with this lesion have been well documented in medical literature. The pathophysiologic mechanism responsible for the late—at at times terminal—symptoms and signs has not as yet been explained satisfactorily.

In 1913 Trotter stated that it was the interference with circulation of the brain by the subdural collection which produced the clinical manifestations. In 1925 Putnam and Cushing concluded that the hematoma, although established immediately after injury, announces its presence when the brain becomes edematous or congested. In 1932 Gardner formulated a hypothesis that the subdural collection slowly increased in size as a result of its high osmotic tension, thereby producing an increment of the mass, and eventually a rise in intracranial pressure. In 1936 Munro and Merritt subscribed to the theory set forth by Gardner and, in addition, stated that the age of the collection could be estimated by a deterioration of the protein content of its fluid, combined with the pathology of the surrounding membrane. In 1941 one of us (Browder) recorded the findings of obvious edema of the brain underlying a long-standing subdural hematoma and suggested a relationship between delayed symptoms and this lesion. In 1943 it was further stated (Browder) that alterations in cerebral circulation, underlying either an organized blood clot or the chronically encapsulated fluid collections, and producing cerebral edema, are the most likely explanation for the latent symptoms. In 1951 an attempt to correlate cerebral edema with the abnormal clinical findings was recorded.

Since this time the results of anatomic, pathologic, electroencephalographic, serial pneumoencephalographic, and serial arteriographic studies of patients with subdural collections have supported the notion that it is the swelling of the brain underlying the subdural hematoma which produces the latent symptomatology.

Discussion

DR. THOMAS I. HOEN: That a subdural hematoma slowly increased in size as a result of hygroscopic activity due to hemolysis and the conversion

of the fluid to one of a very high osmotic tension has long been accepted, but this process does not explain the clinical course of subdural hematomas. I should like to know more concerning the explanation of the edema in the hemisphere underlying the hematoma, and I do not think it necessary to abandon the idea that there is a progressive change in the osmotic hygroscopic activity. We know that the spinal fluid becomes xanthochromic, and there is obviously some chemical transfer going on which may play a role in the production of the alteration of the venous physiology of the hemisphere.

DR. FRITZ CRAMER: It is always a pleasure to hear Dr. Browder present another authoritative analysis in the pathology of traumatic intracranial lesions. I wonder, however, whether the cerebral edema which he has demonstrated here really covers all of the factors which simulate an expanding intracranial lesion in subdural hematoma. I wish to raise a question in respect to this edema and its expansive qualities: If the brain does not expand to fill the space from which the hematoma has been evacuated, and presuming that there is edema present, what is Dr. Browder's concept of the usefulness of injecting air or fluid into the lumbar subarachnoid space to cause the brain to fill the dead space?

DR. ABRAHAM KAPLAN: The most constant sign clinically in chronic subdural hematoma is the fluctuation state of consciousness. Is it due to fluctuations in cerebral edema? After the removal of a subdural hematoma in elderly people, the brain may fail to rise to the level of the dura. If the brain is very edematous, it should rise promptly. I have had experiences in which air studies were carried out prior to surgery, and x-ray studies done immediately after the removal of the hematoma showed prompt ventricular shift back to the side of the lesion. If there were only cerebral edema as an explanation, this could not happen. Further, how is one to explain the homolateral paresis in these patients on the basis of cerebral edema?

DR. GEORGE H. HYSLOP: Has Dr. Browder run across a hematoma with a history going back to a head trauma, apparently an uncomplicated concussion, and then with no symptoms for several years? In the case I encountered there was rapid development of a clinical picture which was labeled that of a glioblastoma. On air study the patient showed a shift to the opposite hemisphere and reduction in the size of the lateral ventricle on the side of the so-called neoplasm. At operation a very old subdural hematoma was found. This particular patient happened to have an effective clinical result, with functional recovery.

DR. FRANCIS ASBURY ECHLIN: I am not sure that I understood Dr. Browder clearly. Will he tell us whether he visualizes a subdural hematoma, after its initial formation, as gradually getting bigger, or does he regard such a hematoma as remaining stationary in size, following its initial formation? If he thinks it is stationary, how does he explain the progressive nature of the changes in the brain: the edema and the vascular changes? Also, why do so many of these patients get better so promptly when we remove the hematoma if the changes that occur are due to a stationary, nonexpanding mass?

DR. E. JEFFERSON BROWDER: I wish to thank the discussers—Drs. Hoen, Cramer, Kaplan, Hyslop, and Echlin. The several questions raised may be logically answered by a correlation of the abnormal clinical features and the pathologic state encountered, namely, a nonexpanding surface mass (subdural collection), chronic intracerebral venous stasis, and consequent focal intracerebral swelling, which frequently extends into the midbrain-hindbrain zone. A major defect in our understanding of the over-all problem is our lack of knowledge concerning the physiological of the transcerebral venous system.

Protentiation of Extrapyramidal Side-Effects by Dextro Amphetamine (Dexedrine) in Psychiatric Subjects Receiving a Phenothiazine Derivative (Trilafon). DR. SIDNEY MALITZ, DR. HAROLD ESECOVER, and DR. BERNARD WILKENS.

Two volunteers, one a psychiatric patient and the other a medical student, developed dyskinesia reactions when dextro amphetamine (Dexedrine) was administered following intravenous perphenazine (Trilafon). The first subject developed spastic torticollis and flexion spasms of the right arm and leg, a half-hour after taking a 15 mg. Dexedrine Spansule. Sixteen hours previously he had received 20 mg. of perphenazine I. V., as a blocking agent against the psychotomimetic effects of LSD-25. The condition was at first misdiagnosed as hysteria by the resident because of its bizarre appearance. The second subject received 5 mg. of perphenazine I. V., and three hours later received 5 mg. of dextro amphetamine disguised in a capsule. Within a half-hour he developed perioral spasms and involuntary protrusion of the tongue. Five days later the same subject received 20 mg. of perphenazine I. V. This time dextro amphetamine was omitted, and the patient did not develop dyskinesia. Both subjects were relieved by 125 to 250 mg. of amobarbital (Amytal) sodium I. V.

It is postulated that dextro amphetamine may potentiate the tendency of phenothiazines to evoke acute extrapyramidal responses. Until further research is done in this area, the authors advise caution in administering amphetamines and phenothiazines simultaneously.

Discussion

DR. DONALD F. KLEIN: Dr. Malitz has presented significant clinical anecdotes suggesting a potentiating action of dextro amphetamine (Dexedrine) on the extrapyramidal effects of perphenazine.

It is known that intravenous epinephrine increases tremor amplitude in naturally occurring Parkinsonism and that amphetamine does the same in monkeys made Parkinsonian by lesions of the midbrain tegmentum. However, in man dextro amphetamine has no marked effect on the tremors and rigidity of Parkinsonism.

I have had contact with two cases of buccoglossal dystonia in opiate-withdrawal syndromes, treated with phenothiazines, during the period of massive sympathetic discharge.

Much experimental work is needed to clarify these complex issues.

PHILADELPHIA NEUROLOGICAL SOCIETY

Frederick Murtagh Jr., M.D., Presiding

Regular Meeting, Feb. 7, 1958

Controlled Pneumoencephalography with Small Amounts of Air in the Diagnosis of Acoustic Tumors. DR. FREDERICK MURTAGH, DR. MICHAEL SCOTT, and DR. H. M. STAUFFER (by invitation).

The principles of controlled pneumoencephalography and the positive pressure technique of air injections have been clearly outlined and used by Robertson and Lindgren. The method has been emphasized by Shapiro, in this country. From 10 to 15 cc. of air injected into the spinal subarachnoid space without the prior removal of spinal fluid will raise the pressure slightly but will not disturb the subarachnoid cisterns or produce a shift of the intracranial structures, the latter being highly dangerous in the presence of an expanding lesion. The method is particularly valuable in the visualization of the cerebellopontile cisterns as a method of ruling out a cerebellopontile tumor. The patient is placed in a sitting position in front of a Potter-Bucky holder, with the head angulated forward 40 degrees with the horizontal beam of the x-ray tube. Fifteen cubic centimeters of air is injected, and the x-ray film is exposed at the end of the injection. This will visualize the cerebellopontile cisterns and demonstrate the presence or absence of a tumor in this region. The procedure is contraindicated in the presence of marked increased intracranial pressure, as indicated by papilledema.

Discussion

DR. MATTHEW T. MOORE: I should like to inquire of Dr. Murtagh how many false-positive and false-negative results he has had with this test.

DR. ROBERT A. GROFF: Dr. Murtagh is to be complimented on this ingenious idea. Partial pneumoencephalography has been done by others, as well as in cases of increased intracranial pressure. When it is done in cases of the latter, I feel that as a precautionary measure burr holes should be placed in position for tapping the ventricles so that if an unfortunate reaction occurs it can be used as an emergency measure. If it is possible to visualize the cisternae in the vicinity of the cerebellopontile angle consistently, I think this test is very valuable. It would appear to me that the test has not been used in a sufficient number of cases to determine its practicality, This brings up the question of whether the author had any false-positive results. It would seem to me that Dr. Murtagh's idea has merit, and therefore deserves further investigation.

DR. HENRY A. SHENKIN: We have used a fractional technique in the diagnosis of chiasmal lesions with great success in the past year and can particularly confirm the statement that this method seldom produces any reaction in the patient.

DR. AXEL OLSEN: There are two suspected cases of acoustic neuroma currently at Philadelphia General Hospital, and we plan on using this test in them.

DR. MICHAEL SCOTT: What impresses me most about this test is the minimal reaction and the fact that an anesthetic is usually unnecessary. Partial encephalography is also helpful in diagnosing lesions in the supratentorial area. I should not recommend this technique in cases with increased intracranial pressure. This procedure may also be of value in visualizing arachnoidal adhesions or obliteration of the cisterna pontis following subarachnoid bleeding or meningitis, particularly if the patient has impaired hearing as a deficit.

Tic Douloureux: Treatment by the Combined Use of Hydrochloric Acid Therapy and Histamine Desensitization. DR. WILLIAM J. HANES (by invitation).

A new medical concept of the treatment of tic douloureux is presented, based on an allergic approach, employing hydrochloric acid therapy orally,

histamine desensitization, and antihistamines. Thirteen cases of tic douloureux and one case of herpes zoster involving the trigeminal nerve are reported. A complete history, physical examination, blood count, and urinalysis were obtained in each case. Because of a previous interest in the therapeutic results derived from HCl orally, gastric analyses were performed on each patient. This study revealed in most cases an absence or decrease in free HCl content, and this finding served as the basis for the reasoning that this therapy was indicated. A theory as to the pathogenesis of trigeminal neuralgia, substantiated by therapeutic results, is proposed, and a practical and simple therapeutic procedure is outlined. Previous effective relief of this agonizing pain has been accomplished only by destroying the ganglion and the sensory nerves surgically, chemically, and by boiling water. The method described herein makes these heroic procedures unnecessary. A follow-up of the cases presented for a period of six months to nine years is included, thus ruling out any likelihood of spontaneous remissions. Five of the patients had recurrences of their pain and were relieved again when the allergic therapeutic approach was used, this being further evidence to support the theory presented.

Discussion

DR. A. M. ORNSTEEN: This paper is an excellent presentation, with all the facts stated clearly and fairly. It would be unfair to contradict some of Dr. Hanes' statements because he has at times pointed out their contradictable nature. Who of us can voice serious objection without comparable experience; and, again, who of us could take nine years to ascertain the value of any particular method? There is much variability in the clinical presentments of tic douloureux. The chief difficulty in this regard is the spontaneous remitting and recurring characteristics of the clinical course, which makes it particularly difficult to evaluate a therapeutic method. I would say that Dr. Hanes' theoretical basis for his therapeutic method cannot be attacked in the face of his results presented in the protocol. Theoretical concepts on this subject vary widely. A basic question in a presentation of this sort is whether all the cases presented suffered typical tic douloureux, or true trigeminal neuralgia. This is merely a pragmatic statement, rather than a doubtful reflection. Any form of therapy that affords relief to the patient is worthy of serious consideration. For quite a while now parenteral vitamin B_{12} therapy has been popular, but latterly it seems to be somewhat on the wane. Dr. Hanes is to be commended on his credibility of motivation in his case of clinical investigation.

DR. CHARLES RUPP: All neurologists are familiar with posterolateral sclerosis, which invariably is associated with achlorhydria. I have never seen a case of tic douloureux associated with posterolateral sclerosis. I have not been too much impressed that the cases presented are those of tic douloureux. In one case the pain came on when the patient was only 9 years of age, and a number of the other patients had the onset very early in life. In my experience, tic douloureux usually occurred in patients in the middle and later years of life. I would like to know how many of the patients presented have been seen by a competent neurologist who corroborated the diagnosis.

DR. SAMUEL B. HADDEN: This bit of clinical research is very significant to me, if for no other reason than the fact that it was not supported by a grant from the U. S. Public Health Service or from some foundation or pharmaceutical company. It was carried out by Dr. Hanes in the course of his practice, with his own patients, and was individually financed. Dr. Hanes has presented his procedure, the rationale of it, and his evaluation of the results. There may be a question of the diagnosis in some of his cases, but there can be little doubt that improvement occurred. Others might not be able to duplicate the results, but this would not imply that Dr. Hanes obtained the results claimed. It would simply demonstrate once more that the confidence and enthusiasm of a true physician who seeks relief for a suffering patient can many times be a most effective therapeutic agent in migraine, tic douloureux, and other such disorders in which there may be a strong functional element.

DR. HENRY A. SHENKIN: We have all listened to various "cures" advocated for major trigeminal neuralgia. These have not held up, and undoubtedly the original reports took advantage of the natural remission rate in this disease and included cases other than true tic douloureux. The present report is based upon a very vague theory, and the treatment is prolonged, so that one may wonder whether the ultimate results will be any different from numerous treatments previously suggested so enthusiastically by their proponents.

DR. HARVEY BARTLE JR.: I have followed Dr. Hanes' work for several years and have had the privilege of seeing one of his patients. Dr. Hanes has shown great perseverance in this study, for which he should be commended. I hope that he may be able to continue this work and report to us again at a later date.

DR. WILLIAM J. HANES: I appreciate both your compliments and your criticisms. I do not claim that this method of treatment is a permanent cure; rather, it is a means of allaying symptoms. If you could see the reactions of these patients who, after experiencing a recurrence of their pain, are relieved within two or three minutes by the use of intravenous diphenhydramine (Benadryl), I feel

sure that you would be impressed. In nine years I have treated 14 cases of tic douloureux, each patient having been referred by a patient previously relieved of this agonizing pain. In answer to Dr. Shenkin, most of the patients reported upon this evening had been seen by neurologists prior to coming to me, one man having been seen by four neurologists, two of whom are present tonight. Finally, after many alcohol injections and a supraorbital avulsion, which failed to give relief, the patient was referred to me, and he responded to the described treatment. Dr. Bayard Horton, of the Mayo Clinic, feels that I have found the solution to this problem from an approach based on disturbed chemistry and physiology. It was Dr. Horton's opinion that if the method of this treatment is worth while, it will last; if not, it will die, as it should.

A Case of Sensitivity to Poliomyelitis Vaccine. DR. MARJORIE A. MEYER (by invitation), DR. RICHARD A. BRUNNER (by invitation), and DR. SAMUEL B. HADDEN.

A 28-year-old married woman complained of generalized weakness and progressive ascending paralysis two hours after receiving her second poliomyelitis vaccination, which followed the first by one month. The paralysis manifested itself by numbness and tingling in the fingers and the toes at the onset, and then by generalized weakness, which became progressively worse, so that the patient was unable to walk and finally could not even turn the pages of a book and had difficulty in breathing. The spinal fluid showed no cells; the spinal fluid culture was negative; the total protein of the fluid was 67 mg. %. Blood and stool specimens were all negative for poliomyelitis virus. X-rays of the chest, entire spinal column, and skull were all negative for malignancy. The remainder of her laboratory studies were all within normal limits. Six months prior to the present illness, the patient had a radical mastectomy and hysterectomy. Eighteen months prior to admission she had had severe mumps and "viral" gastroenteritis. During her hospitalization for her operations, and on several other occasions, she had received penicillin, without any untoward reactions, and had no past history of allergy. The patient was treated with corticotropin. The duration of illness was six weeks, with complete recovery in two months.

Discussion

DR. ANTHONY S. TORNAY: The following experiences concerning poliomyelitis vaccine administration and its sequelae have occurred at the Philadelphia Municipal Hospital. The 4-year-old daughter of a physician was given the vaccine as suggested by the manufacturer, using the first batch of vaccine released; it was not the Cutter vaccine. The child developed severe meningitis and a secondary encephalitis. She had numerous complications and died within 48 hours after admission. The Virus Laboratory reported Type I poliomyelitis virus. The second child admitted was an 8-year-old girl who developed complete paralysis of the left arm following the injection of vaccine in that arm. There was an elevation of the spinal fluid cell count, and the diagnosis of poliomyelitis was established. Rapid recovery occurred in three weeks. The third child was a boy who was admitted with bilateral weakness of the shoulder-girdle muscles. He also had received the vaccine. There was an elevation of the spinal fluid cell count. He recovered rapidly. It is to be noted that the last two patients received the modified vaccine, which was supposed to be produced under a more rigid control.

DR. CHARLES RUPP: Dr. Meyer has presented fairly convincing evidence of an allergic reaction to the vaccine, but I wonder whether she and her co-author have considered the possibility that the patient may have had a mild attack of paralytic poliomyelitis.

DR. SAMUEL B. HADDEN: Dr. Meyer reported this case to you at my request, because it was one in which the patient developed widespread evidence of anterior horn cell involvement after the second injection of poliomyelitis vaccine. It is our belief that the lower motor neuron cells were sensitized by the first injection, and that when the second was given there was an intracellular response, which resembled acute poliomyelitis and which, for a time, presented threatening manifestations. On admission there was widespread loss of power, absence of tendon reflexes, and diminished muscle tone. No sensory changes were ever present. Eventually, muscle wasting became apparent, and there were pathological electrical responses. We have not considered this condition an actual poliomyelitis infection, for there was no elevation of temperature. Onset was sudden, and evidence of widespread involvement developed rapidly. No active virus was found in the spinal fluid. This did not resemble an anaphylactic response. This patient was never acutely ill. No meningeal involvement was noted. It is impossible to determine whether or not her mumps played any role, but we have discarded any thought about her breast cancer having a causal relationship. This case has been reported to call attention to the possibility of a cellular sensitivity developing during immunization against poliomyelitis.

James J. Ryan, M.D., Presiding
Regular Meeting, April 10, 1958

Mesencephalic Stimulation and Reticulotomy in Parkinsonism with Oculogyric Crisis. Dr. Henry T. Wycis and Dr. Ernest A. Spiegel.

The case is presented of a 30-year-old white man suffering for six months from oculogyric crises, lasting 5 to 30 minutes and occurring almost daily. In addition, the patient had a left-sided Parkinsonian tremor and rigidity of six years' duration. Both the crises and the tremor were uninfluenced by medication. By means of stereotactically placed electrodes, stimulation was carried out, and lesions were placed in the central aqueductal gray matter, on the basis of experimental studies by Spiegel and Scala in cats. Stimulation of the periaqueductal gray matter caused a deviation of both eyeballs upward and inward, followed by a vertical nystagmus when the current was discontinued. Lesions in this region produced a temporary paresis of upward gaze and cessation of the oculogyric crises. With a return of normal ocular movements, the oculogyric crises returned but were later definitely reduced by dextro amphetamine, which preoperatively proved ineffective. The patient has had but four attacks during the past six months. In a further operation, guided electrodes were inserted in the mesencephalic tegmentum. Stimulation of this area induced a 6-per-second tremor, which was recorded photoelectrically. Subsequent lesions in this region abolished the tremor in the opposite hand and alleviated it in the opposite leg, and reduced the rigidity in these extremities for the duration of the observation (nine months). The patient's movements, before, during, and after the operative procedures, were demonstrated by motion pictures.

Discussion

Dr. A. M. Ornsteen: Did I understand you to say that the patient was admitted to the hospital with a disease of unknown etiology?

Dr. Henry T. Wycis: There was no history of an encephalitis prior to the development of the Parkinsonian syndrome.

Dr. A. M. Ornsteen: Do you know of any disease that would produce such symptoms other than Parkinson's disease? How long had he had the tremor?

Dr. Henry T. Wycis: He had had the tremor for 11 years. Though an encephalitic origin is probable, it could not be proved by the patient's history.

Dr. A. M. Ornsteen: I know of no other condition causing an oculogyric crisis. How old was the patient at the time he was admitted to the hospital?

Dr. Henry T. Wycis: He was 30 years of age.

Dr. A. M. Ornsteen: And he had had the tremor for 11 years, or since the age of 19? How long had he been having attacks of oculogyric crises?

Dr. Henry T. Wycis: For six months prior to his admission.

Dr. A. M. Ornsteen: The fact that he had had tremors since 1947 and no history of encephalitis indicates that it was sporadic.

Dr. Henry T. Wycis: He may well have had an encephalitis; but, as I said before, it could not be proved.

Dr. A. M. Ornsteen: Your patient developed the first symptoms of a postencephalitic Parkinsonism 11 years ago. I know of a patient who developed Parkinson's disease 13 years after an attack of encephalitis. Since this patient was 19 years old at the time, he must have had a sporadic encephalitis. Has he had any attack of oculogyric paralysis since the operation?

Dr. Henry T. Wycis: He has had only a few minor attacks.

Dr. A. M. Ornsteen: I believe that Dr. Schlezinger wrote a paper on the use of amphetamine (Benzedrine) in cases of Parkinson's disease.

Dr. Gabriel A. Schwarz: I would like to ask what anatomical pathways you have intruded upon and what explanation have you for the tremor change?

Dr. E. A. Spiegel: Dr. Scala and I showed experimentally that the periaqueductal gray matter contains at least part of a system innervating vertical eye movements of cortical origin. In the midbrain tegmentum the lesion may affect centrifugal pathways from the basal ganglia and/or parts of the reticular formation.

Dr. David J. LaFia: We are too close to the work to appreciate truly the contribution that these men are making in this field. I was there at the V. A. Hospital at the time that Dr. Wycis was doing this, and the boldness he displayed impressed me very much. We should all be proud of him. Since the cessation of the oculogyric crises lasted only a few months, I believe that it will be necessary to make another lesion. It is too dangerous to make too large a lesion, and I feel that it is safer to make several smaller lesions.

Dr. Henry T. Wycis: In the first operation we made a single lesion on one side. The second

time we made three lesions on the other side, close to the aqueduct.

DR. A. M. ORNSTEEN: Are we to deduce, then, that in persons with postencephalitic Parkinson's disease we are to keep on making additional lesions?

DR. E. A. SPIEGEL: I should not advise too large lesions in the periaqueductal gray matter. We try to interfere with the pathways from the cortex and/or the basal ganglia to the oculomotor nuclei, but should be aware that the periaqueductal gray may contain only part of these systems.

Hydrothermal Lobotomy, an Operation for Producing Controlled Mental Changes in the Brain of a Mentally Disturbed Person. DR. RUDOLPH JAEGER.

The injection of warm water into the brain was first used, on Feb. 13, 1953, to produce progressive and permanent tranquilization effects. Since that date, 65 cases have been so treated. Initially, a trephine opening is made over the outer convexity of the frontal lobes. These structures are permeated bilaterally with varying quantities of water at 75 C—usually from 2 to 4 cc. Each frontal lobe is injected in three locations with a total of 20 cc. The second treatment is given 10 days later. Subsequent treatments are given by puncturing with a blunt needle into elected parts of the frontal lobes. Quantities sufficient gradually to increase the state of tranquility are injected as improvement progresses. The case material consisted of 18 patients with severe anxiety states; 25 cancer patients with anxiety and pain; 19 patients with intractable pain; one patient with uncontrolled anxiety from apoplexy, and one each with alcoholism and dementia paralytica (paresis). Two patients had senile psychosis, and four were schizophrenic. One death resulted, that of an extremely ill cancer patient. The others had no complications. It is believed by the author that this is a valuable technique in the treatment of painful conditions, as well as abnormal mental states that are uncontrollable by present tranquilizing methods.

Thermal Lobotomy for Mental Disorder and Intractable Pain. DR. LAURENCE M. WEINBERGER (by invitation).

No abstract is supplied.

Discussion

DR. A. M. ORNSTEEN: I can understand the use of this means of therapy in terminal states, but I am puzzled by its use in the 18 cases of anxiety neurosis. What psychiatrist would want that type of treatment for an anxiety state, and what clinical good could result? What about the follow-up on the 18 patients with emotional anxiety states you mentioned? I cannot understand how anyone would have the temerity to destroy brain tissue because of a purely emotional state. This means may be all right for cancer patients, and for schizophrenics in order to restrain them. But what do we get out of this procedure in a psychiatric sense other than to relieve pain?

DR. E. A. SPIEGEL: We have found it wiser to make gradually increasing stereotactic lesions rather than one mass lesion. Some similar attempts have been made in Germany. With this technique one knows exactly where the lesion is placed, and very favorable results have been reported (e. g., Riechert). The question arises, when one is making lesions in the frontal lobe, whether it is immaterial where the lesion is made. Dr. Weinberger and Dr. Jaeger feel that it is immaterial. Anatomical studies by Meyer in England on frontal lobotomies have led to the conclusion that the location of the lesion definitely influences the results. I have another question about the variability in the size and shape of the lesions. How far has this variability been studied for the boiling water method?

DR. NATHAN S. SCHLEZINGER: These papers have been presented with great clarity, and I believe that they have confronted us as psychiatrists and neurologists with the need not to remain speechless. I, too, was startled by the phrase "uncomplicated anxiety states." I hope that this diagnosis was not correct, because I certainly would not advise such treatment for this state. I hope that the patients cited had more than is implied by that phrase. Tranquilizers have been of great value in the treatment of this type of patient. The second presentation brought up the use of this treatment in cases of hopeless malignancy. What survival period was there in these patients? We can hope for other advances in medicine to help cope with this problem of pain. Some other means, it would seem to me, would be preferable to widespread destruction of brain tissue. I believe that we all look forward to the day when there will be no more lobotomies as a therapeutic measure.

DR. MATTHEW T. MOORE: There is still, as Dr. Weinberger pointed out, a hard core of patients who resist any type of treatment along the line of psychotherapy or drug therapy. I, too, hope that a simple anxiety state was not treated with surgery. There are many severely psychotic patients who do yield very nicely to lobotomy. Of our 670 lobotomy patients, 85% responded satisfactorily. Of the schizophrenics, 35% responded satisfactorily. We should not perform any type of destructive procedure without good reason. Most of the work done recently in orthodox lobotomies has been satisfactory. With fractional sectioning, it is possible to avoid any prolonged defects. However, the swing of the pendulum is such that in

time there will be an elimination of all destructive procedures. I agree with Dr. Jaeger as to the temperature of the water. The lesions produced by the method advocated by Dr. Weinberger are so great that there is always the danger that the patients may develop epilepsy. Dr. Weinberger started his work two and one-half years ago, and there may develop cases of epilepsy among those patients treated by him. I know schizophrenic patients who had lobotomies performed in 1947 who are socially adjusted and working today.

DR. ALEXANDER SILVERSTEIN: I wish to question the use of a destructive brain procedure for the "cure" of an anxiety state. The concept of a "cure" for anxiety from brain surgery is also open to question. I have treated several patients for tension depression with severe anxiety who were subjected to transorbital lobotomy. These patients subsequently had recurrent episodes of anxiety depression which responded rather promptly to electroconvulsive therapy. With the lifting of the depression, anxiety and tension also disappeared. I believe the operation recommended by Dr. Jaeger, as well as similar brain operations, should be used only with those chronic psychotic patients who are unmanageable and who have failed to respond to "shock" therapy and administration of adequate amounts of tranquilizing drugs.

DR. THOMAS A. LOFTUS: I have seen several of Dr. Jaeger's patients. He and Dr. Weinberger are doing pioneering jobs. A point that I would like to make is that in some of the cases Dr. Jaeger referred to as anxiety states the diagnosis was really one of a severe depressive reaction. Dr. Ornsteen and the others should be reassured that these could not be correctly termed uncomplicated anxiety states. It was unfortunate terminology. Actually, these persons were very sick patients with an overlay of anxiety.

DR. RUDOLPH JAEGER: I admit that I may have oversimplified the diagnosis in a large group of the cases reported under the term "simple" anxiety state. Actually, they were anxiety states which made the patient unacceptable socially, and many of them were suicidal. I am really not so naïve that I would perform surgical tranquilization on psychoneurotic or psychotic patients who could be cured by psychiatric methods. All of the mentally disturbed patients here reported, with the exception of those with the painful face and cancer syndromes, had received prolonged psychiatric care, without improvement. This procedure is designed to improve the mental state of those patients with severe mental distress who have not, or cannot, be cured by nonsurgical methods. The results have been extremely gratifying, and there is every indication that this therapy is a valuable tool in the management of many psychiatric problems.

DR. LAURENCE M. WEINBERGER: I believe there is a considerable difference of opinion among psychiatrists themselves as to whether or not psychosurgery should be performed. Most psychiatric hospitals have accepted frontal lobotomy in its many forms as an adjunct of good psychotherapy. A total of 20,000 lobotomies have been reported in the last 20 years. This, in itself, indicates that the procedure is a useful one and has stood the test of time. My procedure, and that of Dr. Jaeger's, would indicate that lobotomy as described can be used safely enough and can be performed by a simpler method than the means used in the past. A surgeon does not operate unless psychiatric methods have failed. Therefore, our patients are all refractory to other methods and come to us as incurable problems. Excellent results are not apt to be achieved in this group.

Those patients suffering from cancer who have had massive hydrothermal lobotomy by my method have had a distinct blunting of their spontaneity. They will say that they have pain if asked about it, but there is every indication that it is no longer a distressing condition; nor do they complain to the nurses or family that they need relief from mental or physical distress. Perhaps this can be explained by the fact that the agony of pain is largely psychological.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE PHYSIOLOGICAL BASIS OF NEUROMUSCULAR RELAXATION. E. GELLHORN, A. M. A. Arch. Int. Med. 102:392 (Sept.) 1958.

Animal experimentation studies show that the sympathetic activity of the hypothalamus can be decreased by increasing the afferent impulses from baroreceptors by drugs such as protoveratine and arterenol, with reversal of such effects through sinoaortic denervation, or by decreasing the afferent impulses from proprioceptors by drugs such as succinylcholine and chondodendron tomentosum extract. The decrease in excitability of the sympathetic portion of the hypothalamus is reflected by a reduction in hypothalamic-cortical discharges and a similar reduction in the state of excitability of the cerebral cortex. Clinical correlations involving the relationship of emotional tension and muscular relaxation are obvious. The practical application of the use of drugs increasing intrasinusal pressure for combating emotional tension is difficult, since, like epinephrine, most of these preparations serve to increase tension and anxiety. Arterenol would appear to constitute an exception to this generalization.

PARSONS, Montrose, N. Y.

EFFECT OF PNEUMOENCEPHALOGRAPHY ON FLUID AND ELECTROLYTE METABOLISM. B. L. WISE, R. HILF, and V. J. PILEGGI, A. M. A. Arch. Surg. 77:113 (July) 1958.

The balances for fluid, electrolytes, and nitrogen, as well as urinary steriod excretion and serum electrolyte concentrations, were investigated in three patients before and after pneumoencephalography. There is a transient increase of urinary 17-hydroxycorticoids, but not of 17-ketosteroids. The sodium and nitrogen balance tends to become temporarily negative after pneumoencephalogram. The water balance varies. Occasionally there is oliguria due to increased output of antidiuretic hormone, as a result of stimulation of the supraoptic and paraventricular nuclei.

LIST, Grand Rapids, Mich.

THE PRESENCE OF PHOSPHATIDIC ACID IN ANIMAL TISSUES. L. E. HOKIN and M. R. HOKIN, J. Biol. Chem. 233:800, (Oct.) 1958.

Phosphatidic acids were shown by several lines of evidence to be a normal constituent of mouse brain. These acids contain unsaturated fatty acids. Phosphatidic acids may be intermediates in phosphatide biosynthesis. Also, they may play a part in the mechanisms of active transport across cell membranes.

PAGE, Cleveland.

ACETYLCHOLINE AND THE EXCHANGE OF INOSITOL AND PHOSPHATE IN BRAIN PHOSPHOINOSITIDE. L. E. HOKIN and M. R. HOKIN, J. Biol. Chem. 233:818 (Oct.) 1958.

Guinea pig brain cortex slices incubated with P^{32}-labeled sodium phosphate synthesized five different phosphatides, which were identified. Two additional unidentified redioactive spots were noted. When they were incubated with inositol-2-H^3, the only H^3-labeled phosphatide was monophosphoinositide. The incorporation of inositol-2-H^3 and of P^{32} into monophosphoinositide was increased, and to the same degree, by acetylcholine. Thus, acetylcholine stimulates to about 80% the incorporation of inositol phosphate as a unit into monophosphoinositide. The incorporation of P^{32} into phosphatidic acid by acetylcholine was stimulated 100%.

PAGE, Cleveland.

ACETYLCHOLINE AND THE EXCHANGE OF PHOSPHATE IN PHOSPHATIDIC ACID IN BRAIN MICROSOMES. L. E. HOKIN and M. R. HOKIN, J. Biol. Chem. 233:822 (Oct.) 1958.

Phosphatidic acid is the only recognized phosphatide which incorporates appreciable amounts of P^{32} in cytoplasmic particulate fractions of guinea pig brain under conditions of oxidative phosphorylation. Acetylcholine increases this and was about twice as great in the microsomal fraction as in the other fractions. Atropine abolished the stimulating effect of acetylcholine.

The incorporation of P^{32} was also greatly increased in the presence of sodium fluoride; but, on the contrary, there was no stimulation by acetylcholine of P^{32} incorporation into phosphatidic acid in the presence of fluoride.

PAGE, Cleveland.

THE INCORPORATION OF GALACTOSE INTO GALACTOLIPIDES. R. M. BURTON, M. A. SODD, and R. O. BRADY, J. Biol. Chem. 233:1053, 1958.

Glucose-U-C^{14} and galactose-1-C^{14} are readily incorporated into the neutral glycolipide fraction of rat brain in vivo. The rate of incorporation of the hexoses was correlated with the ages of the animals, and maximal specific activity of the glycolipide fraction was found in rats 10 to 20 days post partum. Maximal specific activity of the neutral glycolipides was observed eight hours after a single intraperitoneal injection of dextrose or of galactose. Twenty-four hours after the injection of the radioactive hexose, the specific activity of the glycolipide fraction had decreased to about one-third that of the maximal value observed (at eight hours).

The experiments conducted in vitro showed that the microsomal fraction of young rat brain contains the enzymes necessary for the incorporation of dextrose and galactose into neutral glycolipides. It was found that uridine diphosphogalactose was the primary hexose donor to a lipid acceptor endogenous to the microsomal fraction. Chromatographic and infrared spectral studies indicate that the radioactive glycolipide isolated from the experiments in vitro is a cerebroside, probably *N*-cerebronyl-O^1-galactosyl sphingosine.

PAGE, Cleveland.

PURIFICATION AND IDENTIFICATION OF BRAIN PHOSPHOLIPIDES ASSOCIATED WITH THROMBOPLASTIC ACTIVITY. D. THERRIAULT, T. NICHOLS, and H. HENSEN, J. Biol. Chem. 233:1061, 1958.

Phosphatidyl serine and lecithin prepared from beef brain exhibited no thromboplastic action, but when the two were dissolved in chloroform, a potent thromboplastic substance resulted.

PAGE, Cleveland.

THE ENZYMATIC SYNTHESIS OF SPHINGOSINE: II. FURTHER STUDIES ON THE MECHANISM OF THE REACTION. R. O. BRADY, J. V. FORMICA, and G. J. KOVAL, J. Biol. Chem. 233:1072, 1958.

Sphingosine appears to be synthesized enzymatically by a reaction concerned with the addition of palmitic aldehyde to the activated methylene carbon atom 2 of serine in the presence of pyridoxal phosphate and manganese ions. "Ethanolamine is not a precursor of sphingosine and does not readily form a Schiff base-metal complex with pyridoxal and Ni^{++} ions. The enzyme preparations used in these studies catalyzed the oxidation of palmitic aldehyde in the presence of diphosphopyridine nucleotide. The conversion of dihydrosphingosine to sphingosine has been observed in an enzyme system obtained from rat brain tissue."

PAGE, Cleveland.

THE ENZYMATIC SYNTHESIS OF INOSITOL PHOSPHATIDE. B. W. AGRANOFF, R. M. BRADLEY, and R. O. BRADY, J. Biol. Chem. 233:1077, 1958.

Tritium-labeled inositol was used to demonstrate the incorporation of inositol into the lipids of a variety of guinea pig tissues, including brain. An enzyme system present in the insoluble residue of guinea-pig-kidney mitochondria is described which catalyzes the incorporation of inositol into inositol phosphatide in the presence of Mg^{++} and cytidine diphosphate choline or cytidine-5′-phosphate. The incorporation of inositol was stimulated by the addition of phosphatidic acids, but not by diglycerides. A mechanism is proposed for the synthesis of inositol phosphatide.

PAGE, Cleveland.

THE γ-AMINOBUTYRIC ACID-α-KETOGLUTARIC ACID TRANSAMINASE OF BEEF BRAIN. C. F. BAXTER and E. ROBERTS, J. Biol. Chem. 233:1135, 1958.

Baxter and Roberts describe a copper chelation method for measuring glutamic acid formation by γ-aminobutyric acid-α-ketoglutaric acid transaminase from beef brain. The enzyme requires pyridoxal phosphate and is inhibited by sulfhydryl reagents. It is not inhibited by anaerobioses or by fluoride, arsenite, cyanide, etc. The protective effects of α-ketoglutarate and pyridoxal phosphate on heat inactivation of the transaminase were shown.

PAGE, Cleveland.

THE ENZYMATIC SYNTHESIS OF SPHINGOMYELIN. M. SRIBNEY and E. P. KENNEDY, J. Biol. Chem. 233:1315, 1958.

An enzyme has been found in chicken liver which catalyzes the transfer of the phosphorylcholine moiety of cytidine diphosphate choline to the free primary hydroxyl group of a ceramide (*N*-acetyl-sphingosine) to form sphingomyelin. The PC-ceramide transferase which catalyzes this reaction is highly specific and is widely distributed in animal tissues. Ceramides seem important as intermediates in biosynthesis of sphingolipides, and it is suggested that they themselves may result from a reaction between sphingosine and a long chain of fatty acid thiolesters of coenzyme A.

PAGE, Cleveland.

THREE-PHASE COUNTER-CURRENT DISTRIBUTION: THEORY AND APPLICATION TO THE STUDY OF STRANDIN. H. L. MELTZER, J. Biol. Chem. 233:1327, 1958.

By use of a technique devised for the distribution of solutes among three immiscible liquid phases, it was shown that the cerebral lipid strandin exhibited at least 15 components in a sample prepared according to published methods.

PAGE, Cleveland.

STUDIES CONCERNING THE COMPOSITION, DISTRIBUTION AND TURNOVER OF PHOSPHORUS IN A PHOSPHATIDO-PEPTIDE FRACTION FROM MAMMALIAN TISSUE. C. G. HUGGINS and D. V. COHN, J. Biol. Chem. 234:257 (Jan.) 1959.

A phosphatidopeptide has been found in brain, heart, kidney, liver, spleen, pancreas, intestine and Ehrlich ascites tumor cells. It is composed of inositol, phosphate-esterified fatty acids, sphingosine or sphingosine-like material, and amino acids, presumably in peptide chains. Studies with radiophosphorus showed the phosphatidopeptide was second only to the acid-soluble fraction as far as specific activity of radiophosphorus was concerned.

PAGE, Cleveland.

Neuropathology

SARCOIDOSIS WITH INVOLVEMENT OF THE PITUITARY GLAND. A. JACKSON and T. R. HOOD, Ann. Int. Med. 49:467 (Aug.) 1958.

Jackson and Hood report the case of a 32-year-old man with proved sarcoidosis as determined by lymph-node biopsy. He subsequently developed evidence of diabetes insipidus, pituitary myxedema, and testicular atrophy. The authors feel that the involvement of the posterior portion of the pituitary is presumably due to sarcoid infiltration.

AIGNER, Rochester, Minn.

RELATIONSHIP BETWEEN EDEMA, BLOOD-BRAIN BARRIER AND TISSUE ELEMENTS IN A LOCAL BRAIN INJURY. I. KLATZO, A. PIRAUX, and E. J. LASKOWSKI, J. Neuropath. & Exper. Neurol. 17:548 (Oct.) 1958.

The authors attempted to correlate by experimental methods the morphologic changes occurring with injury and the altered permeability of the blood-brain barrier, resulting in edema. Initially the trauma was uniformly produced by application of cold to the exposed cortex. Later, sodium fluorescein was used to study the blood-brain barrier. This was injected intravenously 45 to 60 minutes prior to killing the animal. Photographs were taken of the brain in ultraviolet light, and histologic studies were performed. The cats were killed at 6, 12, 24, 48, and 72 hours and 7 and 30 days after injury.

The development of edema was observed within six hours in the white matter underlying the site of cold application. In the area of edema a marked response of the astrocytes was noted within six hours, consisting of marked enlargement of cell bodies and intense PAS-positive staining. Histochemical studies of the latter suggested a glycoprotein nature of the substances involved.

Electrophoretic-pattern study indicated an appreciable increase in the total protein, with striking elevation of albumins in the area of edema.

Fluorescein in the area of injury persisted one month and was associated with the presence of small astrocytes.

In the white matter near the injured area the myelin sheaths were undamaged, but intense astrocytic gliosis was present one month later, where the edema had lasted only a few days.

The findings support the assumption that the astrocytes constitute an important element of the blood-brain barrier.

AIGNER, Rochester, Minn.

ENCEPHALITIS PRESUMABLY OF VIRAL ORIGIN, ASSOCIATED WITH MASSIVE NECROSIS OF THE TEMPORAL LOBE. C. L. ASZKANAZY, M. I. TOM, and L. R. ZELKOWICZ, J. Neuropath. & Exper. Neurol. 17:565 (Oct.) 1958.

Small foci of necrosis of the brain and spinal cord are frequently present in some forms of encephalomyelitis—poliomyelitis, herpes simplex, and the Type B epidemic encephalitides. The authors report seven cases of encephalitis in which large areas of necrosis were localized in the temporal lobes and adjacent regions. It is assumed that the necrosis results from the direct action of the virus and that its localization may indicate the route by which the central nervous system becomes infected.

AIGNER, Rochester, Minn.

IMPORTANCE OF ISCHEMIC DAMAGE TO SMALL VESSELS IN EXPERIMENTAL CEREBRAL INFARCTION. J. S. MEYER, J. Neuropath. & Exper. Neurol. 17:571 (Oct.) 1958.

As part of an extensive study of experimental infarction, Meyer reports on the histological observation of experimental ischemic lesions of the brain, with special reference to ischemic changes in small vessels. The lesions were produced in monkeys and cats by clamping the middle cerebral artery with and without anticoagulants for purposes of comparison. A skull window was used for observation of pial vessels and measurements of cortical oxygen tension during life.

The pathological study of the brains showed that infarction is the result of ischemic anoxia producing damage to both neural and vascular tissues in the supply of the occluded vessel. The severity and anatomical distribution of the infarct depended on the functional adequacy of the collateral circulation. This could be controlled by manipulating the blood pressure and occluding major collateral vessels in addition. Reduction of the cortical oxygen tension to 5% to 20% of normal for one hour or more in the territory of the supply of the occluded vessel resulted in severe infarction.

It was found that propagation of the thrombosis from the site of the arterial occlusion did not occur but, rather, that anoxic changes occurred at the area of junction of the principal collateral vessels. Early, these changes consisted of perivascular edema and clumping of erythrocytes and platelets. Diapedesis and perivascular hemorrhage resulted when blood flow was resumed in damaged vessels. Later, necrosis and phagocytosis of vessels occurred, and those vessels that escaped showed endothelial hyperplasia, which impaired collateral flow. Anticoagulants decreased the agglutination of erythrocytes and platelets and improved local blood flow but resulted in increased perivascular hemorrhage.

In the healing stages of infarction, the collateral circulation was increased by regeneration of small vessels at the edge of the lesion.

AIGNER, Rochester, Minn.

INTRACRANIAL TERATOMA OF A NEWBORN. H. P. CHEN, J. Neuropath. & Exper. Neurol. 17:599 (Oct.) 1958.

Chen presents the case report of a newborn female infant who died at 16 days of age with hydrocephalus. At autopsy a 7 cm. mass was seen to occlude the aqueduct of Sylvius. It contained tissue derived from the endodermal layer, in addition to ectodermal and mesodermal tissue.

AIGNER, Rochester, Minn.

PERSISTENT CAROTID-BASILAR ANASTOMOSIS. J. KEPES and J. W. KERNOHAN, J. Neuropath. & Exper. Neurol. 17:631 (Oct.) 1958.

The authors present the 24th recorded case of a persistent carotid-basilar anastomosis, found incidentally in a 67-year-old woman who died of cancer of the liver and hepatic insufficiency. No other vascular anomaly was apparent.

AIGNER, Rochester, Minn.

ATRESIA AND STENOSIS OF THE AQUEDUCT OF SYLVIUS WITH COMMENTS ON THE ARNOLD-CHIARI COMPLEX. B. W. LICHTENSTEIN, J. Neuropath. & Exper. Neurol. 18:3 (Jan.) 1959.

Lichtenstein discusses the causes of functional inadequacy of the aqueduct of Sylvius; the most crucial site in the intracerebral cerebrospinal fluid pathway, since its functional decomposition leads to dilatation of the lateral and third ventricles, as well as a number of associated pathologic alterations.

Three groups are distinguished: (1) aqueductal dysplasia, or atresia, forking and gliosis; (2) traction stenosis—the elongation and narrowing of the aqueduct as observed in the ma-

jority of instances of Arnold-Chiari complex complicating myelomeningocele, and (3) pathologic processes involving the lumen of the aqueduct, its ependymal lining, or neighborhood structures, leading to its insufficiency. The first two groups are discussed in detail.

Atresia is felt to be a malformation varying from the absolute state which produces hydrocephalus in utero, with pressure disintegration of the convexity of the cerebral hemispheres, to minor asymptomatic degrees.

The author discusses 17 cases of myelomeningocele complicated by progressive hydrocephalus in which the Arnold-Chiari complex was present and the aqueduct was dilated, the obstruction occurring on the fourth ventricle. In nine cases the aqueduct was elongated and narrowed without atresia, and the stenosis of the iter was focal point of obstruction. In six cases the aqueduct was atretic.

The author discusses the Arnold-Chiari complex in infants and adults. The complex occurring in infants and children is characterized by elongation of the pons and medulla, occlusion of the fourth ventricle by cerebellar folia and choroid plexus, and displacement of the medulla and inferior cerebellum into the cervical spinal canal. A significant associated finding in the majority of cases is the vertical narrowing and elongation of the nonatretic aqueduct of Sylvius, which is the focal point of obstruction in the intracerebellar flow of cerebral spinal fluid. The Arnold-Chiari complex in adults is seen with platybasia and/or basilar impression or without obvious cause. Its developmental dynamics and histology also differ from those of the former.

AIGNER, Rochester, Minn.

PATHOARCHITECTONIC STUDIES OF CEREBRAL MALFORMATIONS: III. ARRHINENCEPHALIES (HOLOTELENCEPHALIES). P. I. YAKOVLEV, J. Neuropath. & Exper. Neurol. 18:22 (Jan.) 1959.

Yakovlev reviews the organogenetic malformations known as the arrhinencephalies. These result from a failure of cleavage of the prosencephalon into the paired optic vesicles, olfactory bulbs, and cerebral hemispheres. The syndrome consists of (1) the prosophorinal malformations (harelip, cleft palate, microphthalmia), (2) absence of the olfactory bulbs and tract (hence the term arrhinencephaly), and (3) failure of cleavage of the cerebral hemispheres, with a resulting telencephalon in the form of a holosphere with a single ventricular cavity, instead of two hemispheres with symmetrical lateral ventricles. The common demoninator of these malformations is the failure of evagination of the secondary telencephalic vesicles and of cleavage of the prosencephalon. Such holotelencephalies, as such typical malformations are properly called, are common, and a detailed anatomic and histologic summary of 10 cases is presented.

The author begins his discussion with a definition of malformations as deviations in form and structure induced during the process of development. There are two broad categories of malformations: the first histogenic in type, in which the differentiation of tissue elements—the nerve cells, glia, and blood vessels—is abnormal; and the other, known as organogenic, resulting when the program of development is curtailed and disturbed, without deviations in histogenesis of tissue cells other than the persistence of the embryonal architectonic features. Malformations of the former category include neurofibromatosis, tuberous sclerosis, and the Sturge-Weber angiomatosis, are often familial and hereditary, and show a tendency to produce blastomatous tumors or hamartomas. The latter are rarely hereditary, occur sporadically, and do not show a tendency to produce tumors. Such malformations are spina bifida, anencephaly, the Arnold-Chiari deformity, and the like.

The organogenetic malformations represent curtailment of one or more of the three basic processes of organogenesis of the nervous system—the process of migration of neuroblasts, failure of which results in heteropias; the process of fusion of the lips of the neural plate into the neural tube, failure of which results in dysraphic states, and, finally, cleavage of the prosencephalic portion into the paired optic vesicles, olfactory bulbs, and cerebral hemispheres, failure of which results in the arrhinencephalic group of malformations as the classical prototype.

AIGNER, Rochester, Minn.

DYSRAPHIC STATES. C. E. BENDA, J. Neuropath. & Exper. Neurol. 18:56 (Jan.) 1959.

Among the congenital malformations of the nervous system, errors of fusion of the chorda or cleft formations play a major role. In addition to involvement of the nervous system, there are often associated severe defects in osseous, cutaneous, and fibrous structures,

resulting in cranium bifidum, spina bifida, meningomyeloceles, herniations of the brain, and sequestration dermoids.

Rachischitic defects are frequently associated with hydrocephalus, of which two types have been given widespread recognition: the Arnold-Chiari malformation and the Dandy-Walker syndrome, or the so-called "atresia of the foramen Magendie." Errors in fusion result not only in manifest cleft formations but in various forms of myelodysplasias and dysraphic states.

The symptom complex "status dysraphicus" indicates inadequate or abnormal midline fusion of the developing neural tube. The pathology manifests itself in cutaneous mesodermal and neural pathology, ranging from spina bifida occulta to the severe conditions of cranium bifidum and the various forms of meningoceles and meningomyeloceles, and is also associated with a number of constitutional anomalies.

Ten cases of myelodysplasia are described, three showing the Arnold-Chiari malformation and two the Dandy-Walker syndrome. In five cases myelodysplasia occurred independently of manifest anomalies or cleft formations.

Although these disorders occur most frequently at the level of the lower back or in the cerebellar areas, since they close last in the process of fusion of the neural tube, the levels between are more or less severely involved by an amazing variety of anomalous conditions. These range from micromyelia, heterotopia of the gray and white matter, hydromyelia, and true syringomyelia to states of araphism.

The author suggests that there is some truth in the theory that constitutional inadequacies of mind and body are often suggested by certain physical "stigmata," the significance of which is still little understood.

AIGNER, Rochester, Minn.

CONGENITAL VASCULAR ANOMALIES AND THEIR HISTOPATHOLOGY IN STURGE-WEBER-DIMITRI SYNDROME: NAEVUS FLAMMEUS WITH ANGIOMATOSIS AND ENCEPHALOSIS CALCIFICANS. I. ROIZIN, G. GOLD, H. BERMAN, and V. I. BONAFEDE, J. Neuropath. & Exper. Neurol. 18:75 (Jan.) 1959.

The authors suggest that vascular malformations should be divided into three groups: (*a*) angiomatous, (*b*) aneurysmal, and (*c*) angioblastic. In considering the first group, they selected the Sturge-Weber-Dimitri syndrome to discuss in detail, as it represented an outstanding illustration of congenital vascular anomalies involving primarily the central nervous system.

Twelve cases were studied clinically. Seven were male and five female. The most outstanding and consistent features of the syndrome are port-wine nevi, ocular involvement, epileptic seizures (frequently associated with various neurologic and mental disorders), and meningocerebral angiomatoses.

In eight cases the port-wine nevus (nevus flammeus) was bilateral in the face, and in five the nevus involved also other parts of the body. Therefore the assumption that the nevus flammeus has a trigeminal distribution is not valid.

Ocular involvement is frequent and is usually represented by glaucoma and/or buphthalmos.

All patients had some form of seizures—chiefly grand mal. The EEG was usually diffusely abnormal. Motor and sensory disturbances, trophic changes, and pathological reflexes also appeared. The average IQ was rather low, and emotional instability was evident.

The angiomatoses consisted of congenital vascular malformations which originate as the authors suggest, during the third stage of embryonal vascular differentiation (Streeter). These lesions were also found in extraneural locations, but the vascular calcifications were limited to the cerebral tissues.

Incomplete and abortive forms also have been observed.

The authors propose the name nevus flammeus with angiomatosis and encephalosis calcificans, as it incorporates the fundamental clinicopathological findings and avoids the confusion created by the various synonyms, which frequently describe only certain aspects of the disease process.

AIGNER, Rochester, Minn.

SMALL VASCULAR MALFORMATIONS OF THE BRAIN: THEIR RELATIONSHIP TO UNEXPECTED DEATH, HYDROCEPHALUS AND MENTAL DEFICIENCY. O. T. BAILEY and J. S. WOODARD, J. Neuropath. & Exper. Neurol. 18:98 (Jan.) 1959.

Small vascular malformations of the brain have more frequently been recognized in recent years as possible sources of intracranial hemorrhage, especially in young people. The authors

report cases demonstrating the range of clinical phenomena associated with these small vascular lesions.

Subarachnoid hemorrhage due to rupture of small vascular malformations is found in children and young adults who have died unexpectedly with few premonitory signs or symptoms. The lesion is located deep, and an intracerebral hematoma is produced prior to rupture into the subarachnoid space. The malformations are seldom over 5 mm. in diameter, and their presence is established only by histologic study. It is doubtful whether angiography can demonstrate such lesions. Occasionally the lesion occurs in a region where there are localizing signs, and surgical extirpation may be achieved. Two cases are briefly presented.

Intraventricular hemorrhage may occur with lesions near the ependymal surface, and one such case is discussed.

A rather different mechanism is found when a small malformation occurs beneath the ependymal lining of the aqueduct of Sylvius. Partial or complete obstruction may occur resulting in hydrocephalus from mechanical effects on a small, but vital, anatomic structure. Clinical identification of such patients is difficult or impossible. One case is discussed.

In certain patients with a history of mental deficiency small focal vascular malformations are found scattered throughout the brain. It would be doubtful whether such lesions per se are to be correlated with this status or are regarded as one part of a more complex process.

AIGNER, Rochester, Minn.

ANTENATAL AND PARANATAL CIRCULATORY DISORDERS AS A CAUSE OF CEREBRAL DAMAGE IN EARLY LIFE. C. B. COURVILLE, J. Neuropath. & Exper. Neurol. 18:115 (Jan.) 1959.

Courville discusses his views on the subject of circulatory disorders of intrauterine life, birth, and the postnatal period as the cause of cerebral lesions of early life. These lesions were evidently responsible for the clinical states of cerebral palsy, mental deficiency, and epilepsy, either singly or in combination.

The intrauterine disturbances of circulation which affect the fetal brain are those influencing the maternal circulation or those which occur secondary to structural changes in the placenta. The former include anemia, toxemias, and hypoglycemia. The latter include infarction and syphilis of the placenta and, more commonly, abruptio placentae or placenta prævia.

In the birth process the commoner circulatory disturbances likely to affect the fetal brain are hemorrhage into the fetal cranial space and anoxemia due to various causes.

Postnatal circulatory disturbances as a cause of cerebral damage are probably not significant but may occasionally occur as the result of arterial occlusion.

The author indicates several specific brain lesions which have been suspected of having a circulatory origin. They include (1) general cerebral atrophy; (2) diffuse cerebral cortex lesions, such as (*a*) cortical-subcortical degeneration, (*b*) widespread cortical softenings, and (*c*) subtotal or total cerebral softening; (3) the various individual lesions grouped under the term nodular cortical atrophy, which includes focal cortical scars, sclerotic microgyria, lobar sclerosis and sclerosing hemispheral atrophy; (4) porencephaly; (5) chronic cystic degeneration of the cerebral white matter; (6) diffuse sclerosis, and (7) certain striatal disorders, including status marmoratus and status dysmyelinisatus.

AIGNER, Rochester, Minn.

SEQUELAE OF PERINATAL TRAUMA. N. MALAMUD, J. Neuropath. & Exper. Neurol. 18:141 (Jan.) 1959.

Malamud studied 162 chronic cases with demonstrable evidence of brain damage acquired either at birth or during infancy and early childhood. These lesions were etiologically and pathoanatomically of a nonspecific nature. Specific entities, such as toxoplasmosis, kernicterus, virus infections, heredodegenerative disorders, and sequelae of vascular diseases, were excluded.

Two fundamentally different patterns of lesions were distinguished: 1. A group with primary subcortical pathology. These changes were characterized by status marmoratus of the striatum and thalamus and/or by primary sclerosis or cystic degeneration of the cerebral white matter. 2. A group in which the primary change was in the cerebral cortex, irrespective of whether the lesion was sclerotic or cystic.

It was noted that two different types of history correlated respectively with the two contrasting patterns of lesions. With the first group there was a definite or a probable history of birth trauma in 86% of the cases. In the second group the history in 90% was one of normal birth and early development, followed by an acute illness, occurring some time during infancy or early childhood.

The author advances the opinion that the fundamental lesion in birth trauma is the primary involvement of the white matter and/or basal ganglia, and that the changes are largely restricted to the dorsal parts of the cerebral hemispheres. These stereotyped lesions, regardless of variable circumstances of etiology, suggest that a uniform pathogenic mechanism is responsible in all cases. The location of the lesion can best be explained by assuming a disturbance in the territory of the Galenic venous system.

AIGNER, Rochester, Minn.

DEMYELINATING DISEASES WITH SPECIAL EMPHASIS ON THE METACHROMATIC TYPE (POSTNATAL AND EARLY INFANTILE). I. FEIGIN, J. Neuropath. & Exper. Neurol. 18:156 (Jan.) 1959.

Pathologically, diffuse sclerosis is characterized by the presence of broad zones of degeneration affecting the major portions of the central white matter of the cerebrum. The cortex and the basal ganglia are not affected, although the cerebellar white matter and the tissues of the brain stem may be.

Microscopically, the most striking change is the loss of myelin sheaths in broad uniform areas with relative preservation of the axons and neurons. The latter is seen in other demyelinating diseases also. The glial reactions are variable. The tissue reactions may result in very heterogeneous pathologic patterns—with greatly varying lesions in different portions of the degenerating areas within the same case, as well as in different cases within this group.

Recent interest suggests the possibility that diffuse sclerosis might represent an abnormality of lipid metabolism. In this group the term "leucoencephalopathy" is often applied. The more specific metabolic character of the process is indicated by the presence of abnormal materials in the tissue which are not generally noted in other circumstances. Some of these are metachromatic.

Metachromatic materials are those which are stained by selected dyes a color distinctly different from that of the dye itself—therefore with toluidine blue most materials appear blue, but the metachromatic materials appear pink or violet.

In diffuse sclerosis the metachromatic deposits generally appear in clusters of granules up to 3μ in diameter. The material may not be homogeneous even within the same case. There is much to suggest that this metachromatic material is not a single substance but a mixture of related substances, differing in many histochemical properties. Metachromatic materials are found in other diseases, not necessarily related to demyelinating diseases. It is possible in some instances that they represent an abnormal intermediate in myelin formation. The pathogenesis and metabolic relationships of diffuse sclerosis remain to be clarified.

AIGNER, Rochester, Minn.

STUDIES ON KERNICTERUS: RELATIONSHIP WITH SULFONAMIDE INTOXICATION; REPORT ON KERNICTERUS IN RATS WITH GLUCURONYL TRANSFERASE DEFICIENCY AND REVIEW OF PATHOGENESIS. W. A. BLANC and L. JOHNSON, J. Neuropath. & Exper. Neurol. 18:165 (Jan.) 1959.

This study is divided into three sections. The first deals with the pathological anatomy of Gunn's rats—a strain with familial hyperbilirubinemia, in which kernicterus occurs. These animals are deficient in their ability to convert indirect bilirubin into direct-acting bilirubin by the fixation of two molecules of glucuronic acid to the former. This usually takes place in the liver and requires the enzyme glucuronyl transferase. This deficit is awkwardly called hypoglucuronyltransferasia. In the homozygous animals hyperbilirubinemia develops within a few hours of birth. Kernicterus develops only during the first three weeks in about 65% of the jaundiced animals. Some survive to adulthood with persistence of central nervous system damage. Clinical signs usually do not appear before the age of 7 days and are first extrapyramidal signs with ataxia and incoordination, followed later by hypotonia, irritability, weight loss, and episodes of athetosis, opisthotonos, and clonic convulsions, followed by death in the third to the fourth week. One-half the jaundiced survivors have neurologic sequelae. No hemolytic component was shown.

Homozygous animals all showed macroscopic pigmentation of the brain of all rats dying in the acute stage of kernicterus. Staining varied proportionally with the intensity of the icterus and the severity of the clinical symptoms. The pigmentation was diffuse—especially in the hippocampus and thalamus—but rarely in the cortex. The earliest detectable changes in ganglion cells were associated with the presence of intracellular bilirubin, which is compatible with the concept that bilirubin is the toxic agent.

The second part of the paper deals with sulfonamides and kernicterus. Sulfisoxazole (Gantrisin) had no toxicity in the newborn rats, nor did it alter the blood-brain barrier. Such treatment produced a drop in the bilirubinemia and was accompanied by an increase in icterus of all tissue, suggesting that the drug induced a shift of bilirubin from the vascular component into the extracellular fluid.

The third section deals with the pathogenesis of kernicterus. The conditions associated with it are discussed under three main headings, anoxia, bilirubin toxicity, and the blood brain-brain barrier permeability to bilirubin. It is suggested that an increase in a diffusible form of bilirubin, with a shift of this compound from the circulating blood to other body compartments, is one of the common denominators in the different conditions leading to kernicterus. According to this concept, unconjugated bilirubin is itself the toxic agent producing nerve-cell necrosis.

AIGNER, Rochester, Minn.

REMOVAL OF THE CAUDATE NUCLEUS. B. N. KLOSOVSKII and N. S. VOLZHINA, Fiziol. zhur. 42:817-819, 1956.

Chronic experiments (two to three years) with bilateral removal of the nucleus caudatus (with preservation of the cerebral cortex) did not confirm the prevalent opinion that blood pressure, respiration, vestibular function, nutrition, and growth depend on the nucleus caudatus; the alimentary, play, sexual, maternal, and other instincts were preserved (in puppies); their behavior, though disturbed, became normal a month later. Nevertheless, the conditioned reflex activity remained disrupted: No reflexes (1,200 combinations) could be elaborated. Unilateral removal of the nucleus caudatus in puppies did not result in asymmetry in the body build and the extremities; the behavior of the animals remained unchanged, and only the period for elaboration of conditioned reflexes became longer. Section of the corpus callosum or the internal capsule or the removal of the anterior hemispheres of the brain failed to cause behavior disturbances. Section of the corpus callosum likewise did not interfere with the elaboration of conditioned motor reflexes. The authors draw the conclusion that the conditioned reflex activity depends on the caudate nuclei.

CHANGES IN THE NERVOUS SYSTEM FOLLOWING CARDIAC ARREST. G. A. AKIMOV, Vestnik khir. 5:80-86, 1957; Ref. 32.

The author studied 22 patients who suffered cardiac arrest lasting from 2 to 75 minutes during deep intratracheal anesthesia. There were 15 men and 7 women, and their ages varied from 4 to 61 years. Ten patients died 5 to 48 hours later. A detailed description is given of the neurological symptoms following upon the arrest of the heart and, subsequently, upon the resumption of its activity. Pathoanatomical examination of the nervous system of those patients who died revealed no macroscopic changes. Microscopic study established the presence of edema of the brain and meninges, with marked vascular changes and diffuse and focal degenerative changes in the nerve cells, with areas of necrosis. Changes were also noted in the fibers and nerve endings of the central and peripheral nervous system. The causes of the cardiac arrest were varied. Experiments on dogs and cats demonstrated, in agreement with other investigations, that hypothermia has a beneficial influence on the stability of the nervous system when the heart is excluded from the circulation. The nervous system is exclusively sensitive to insufficiency of oxygen.

Meninges and Blood Vessels

MENINGITIS DUE TO MIMA POLYMORPHA. H. L. FRED, T. D. ALLEN, H. L. HESSEL, and C. F. HOLTZMAN, A. M. A. Arch. Int. Med. 102:204 (Aug.) 1958.

The authors present the fifth reported case of a patient with meningitis caused by Mima polymorpha, a Gram-negative coccobacillus closely resembling Neisseria. A favorable response was obtained with massive penicillin therapy. The authors emphasize the frequency of hemorrhagic phenomena (skin and adrenals) in the fatal cases.

PARSONS, Montrose, N. Y.

RUPTURED ANEURYSM OF THE CIRCLE OF WILLIS ASSOCIATED WITH POLYCYSTIC KIDNEYS. S. W. GROSS and M. SPRING, A. M. A. Arch. Int. Med. 102:806 (Nov.) 1958.

Gross and Spring report the case of a 42-year-old woman who died of uremia due to bilateral polycystic kidney approximately four years following successful ligation of the common carotid artery for ruptured aneurysm of the right internal carotid artery. The frequency of other developmental defects, such as polycystic kidneys (6%) and coarctation of the aorta

occurring in association with intracranial aneurysms, is emphasized. The relatively favorable long-term effects on intracranial aneurysms of reduction of intracranial carotid systolic pressure through cervical-ligation procedures is contrasted with the less encouraging results of conservative nonsurgical management.

PARSONS, Montrose, N. Y.

THE PRACTICAL VALUE OF THE INTERNAL CEREBRAL VEIN IN THE ANTEROPOSTERIOR PHLEBOGRAM. F. MURTAGH and H. M. STAUFFER, Am. J. Roentgenol. 80:978 (Dec.) 1958.

Murtagh and Stauffer point out that displacement of the internal cerebral vein is a sensitive indicator of the presence of a unilateral intracranial tumor mass, particularly if the mass is located in or near the temporal lobe. Displacement of the cerebral vein is determined by taking stereoscopic films in the anteroposterior projection during the venous phase of filling when performing cerebral angiography. Each internal cerebral vein runs in the roof of the third ventricle, about 1 mm. lateral to the midline. The cerebral veins lie well below the edge of the falx cerebri and anterior to the tentorium cerebelli, so that they are more subject to displacement than is the pineal gland, which is somewhat fixed by these structures. Mass lesions of the frontal lobe produce maximum lateral displacement of the anterior cerebral artery, with little or no shift of the internal cerebral vein. Maximal displacement of the vein occurs with masses in the temporal lobe or midhemisphere, which usually produce a less pronounced degree of displacement of the anterior cerebral artery. A mass in the parietooccipital region is usually considered in a "blind" area for carotid angiography, but such a mass will produce lateral displacement of the deep cerebral vein with no lateral displacement of the anterior cerebral artery.

WEILAND, Grove City, Pa.

DISSECTING ANEURYSM OF THE INNOMINATE ARTERY WITH BONE FORMATION COMPLICATED BY CEREBRAL INFARCTION. H. F. ROBERTSON, C. ELLOSO, G. KUZMISHIN, and D. LEVITT, Ann. Int. Med. 49:1415 (Dec.) 1958.

The authors discuss a case of dissecting aneurysm of the innominate artery as an entity which had not previously been reported in the literature.

Their patient was a 69-year-old woman who was in good health until five hours prior to admission, when she developed a sharp pain in the right temple, followed by weakness and dizziness, and later by nausea and vomiting. On examination, the right pupil was found to be dilated, and a slight left facial weakness was present and the tongue deviated to the left. There was total sensory loss and weakness of the left side of the body. The reflexes were equal and active. Rales were present, and the liver was enlarged. The following day the patient became semicomatose. The reflexes on the left were absent, as was the left corneal reflex. The right lid was ptosed and the pupil pinpointed. The patient did not change appreciably, and she died on the 17th hospital day.

Autopsy showed a dilated innominate artery which contained a large antemortem thrombus, present within the media and compressing the lumen. A cystic cavity was also found in the right temporal lobe, measuring up to 4.5 cm. in diameter.

The authors suggest a careful history and physical examination, correlated with x-rays; and specific studies, such as angiocardiography and retinal-artery pressure determination, may afford the opportunity to make an antemortem diagnosis. They suggest the external (cervical) and internal (pharyngeal wall) palpation of the carotid artery in all instances of hemiplegia, as this may lead to one causative factor, as reported.

AIGNER, Rochester, Minn.

INTRACRANIAL ANEURYSM IN THE GERIATRIC PATIENT. E. A. SMOLIK and F. J. NASH, J. A. M. A. 167:931 (June 21) 1958.

Studies have shown that atherosclerotic vascular lesions are not uncommon at the site of origin of arteriosclerotic aneurysms. As people live to an older age, with accompanying vascular changes, aneurysms of this origin may become more frequent. Smolik and Nash demonstrated intracranial aneurysms in three patients, aged 66, 76, and 77. Because of the unendurable pain and advancing neurologic deficits, surgical intervention became mandatory.

In cases of suspected intracranial aneurysm, cerebral angiography is required to establish the diagnosis. Advanced age per se, is not a contraindication if the technique employed is the percutaneous carotid puncture, under thiopental anesthesia, and the use of 50% diatrizoate solution as the contrast medium.

Carotid ligation was successfully employed in two of the three cases. These patients were completely free of pain and regained oculomotor nerve function after treatment by common carotid artery ligation on the involved side. In each case the Poppen-Blalock clamp was used for controlled carotid occlusion. The third patient, aged 77, died 30 days after total arterial occlusion. No autopsy was permitted.

ALPERS, Philadelphia.

Diseases of the Brain

ENCEPHALOPATHY IN PULMONARY DISEASE. H. BACCHUS, A. M. A. Arch. Int. Med. 102:194 (Aug.) 1958.

Bacchus reports two cases of pulmonary disease, one interstitial pneumonia and pulmonary arteriosclerosis and the other emphysema and congestive heart failure, in which signs of increased intracranial pressure developed during hospitalization. Autopsy in one case revealed essentially normal nervous system findings. Both patients presented the classical clinical picture of increase intracranial pressure plus laboratory findings, consisting of secondary polycythemia and markedly reduced cerebrospinal fluid proteins, as well as evidence of pulmonary disease and hypercapnia. The authors attribute the increased intracranial pressure to intracranial vasodilatation caused by the hypercapnia and anoxia secondary to pulmonary defects in ventilation or diffusion. The importance of differentiating this cardiopulmonary encephalopathy from brain tumors, hypoglycemia, and cerebrovascular accidents is stressed.

PARSONS, Montrose, N. Y.

INFECTIOUS DISEASES—ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS. H. REIMANN, A. M. A. Arch. Int. Med. 102:217 (Aug.) 1958.

Reimann stresses a number of recent developments of neurological interest in this review of progress in the field of infectious diseases. Experience with the use of the Salk vaccine has demonstrated its effectiveness in reducing the incidence of paralysis in poliomyelitis, especially in patients below the age of 20. Its effectiveness is estimated at about 75%. Its contribution to the prevention of mild infections is less apparent. However, the suggestion that the severity of poliomyelitis has been reduced by the administration of the vaccine will still have to be confirmed after a review of the long-term trend of the disease, as previous studies have shown that certain years, such as 1938, have had an unusually low mortality rate, comparable to that of 1956. The problem of differentiating poliomyelitis from the manifestations produced by Coxsackie and ECHO viruses poses a challenge. The Coxsackie virus syndrome is gradually emerging and consists of acute peri- and myocarditis, meningitis, pleurodynia, herpangina, and parotitis. The ECHO viruses, especially Type 9, may cause a meningitis associated with a rubelliform rash. A new idiopathic diagnostic entity, so-called benign myalgic encephalomyelitis, is described, and the symptoms include myalgia, muscle pareses associated with electromyographic changes, cranial nerve involvement, and systemic symptoms. The incidence is particularly high among hospital workers, and many of the features suggest neurasthenia.

Cat-scratch disease has been noted to exhibit neurologic sequelae of a transient character, consisting of encephalopathy, myelitis, and radiculitis.

Once again, the important role of rabies disseminated by bats, especially in Florida, is stressed. A particularly disturbing feature is that over 50% of the infected bats fail to develop Negri bodies.

A rather detailed study of over 200 patients with herpes zoster has confirmed certain familiar features of this condition, including the predilection for more severe, persistent involvement in older persons. The incidence of generalized disease often associated with lymphoma is somewhat commoner in children.

Insofar as bacterial disease is concerned, the mortality of tuberculous meningitis treated with streptomycin and PAS has fallen from 84% to 54% following the use of isoniazid. Intrathecal therapy is not indicated. Steroid therapy is clearly indicated in tuberculous meningitis, and in no other form of tuberculosis.

Insofar as tetanus is concerned, supportive, rather than antibiotic, therapy has been instrumental in reducing the death rate from 57% to 27%. Cortisone is strictly contraindicated in tetanus, as there is evidence of its inhibition of the antitoxin and its facilitation of the toxin in experimental studies with unprotected animals.

The major role of persons with postdiphtheritic paralysis in the dissemination of diphtheria is stressed. The authors point out that the development of a meningitis following or accompany-

ing pneumonitis in debilitated patients suggests the possibility of Klebsiella involvement. The therapy consists of sulfonamides with other antimicrobials.

Autopsy findings in a case of botulism consisted of petechial hemorrhages in the gastric mucosa and multiple thromboses of the meningeal vessels.

The investigations surrounding the possibility of a spirochetal etiology for multiple sclerosis continue, and a recent investigation reported the cultivation of such organisms from the spinal fluid of 78% of 76 patients, using a new culture medium. None were cultured from 28 unafflicted persons. The belated development (often many years following primary invasion) of cerebral manifestations of cysticerosis is stressed, and a new broad-spectrum anthelmintic, dithiazanine, was introduced in its treatment.

PARSONS, Montrose, N. Y.

ACUTE CEREBELLAR ATAXIA OF UNDETERMINED ORIGIN IN CHILDHOOD. D. N. WALCHER and A. T. ROSS, A. M. A. J. Dis. Child. 96:278 (Sept.) 1958.

Walcher and Ross report on 20 children from 9 months to 8 years of age with a syndrome characterized by the abrupt onset (a day or so) of cerebellar ataxia without evidence of involvement of structures other than the cerebellum and with improvement (to recovery) occurring over several days or weeks after the onset. Two children had nystagmus. Only one child had a residual deficit of mild ataxia and petit mal. Two patients had replases. Systemic reactions were absent or minimal, although headache, vomiting, irritability, and listlessness frequently preceded the ataxia by a few days or accompanied the onset. The cerebrospinal fluid contained 0 to 10 leukocytes in 12 instances, 10 to 25 cells in 3 cases, and 67 to 750 cells in the remaining 5 cases. Lymphocytes predominated. The total protein was below 50 mg. % in 14 cases and between 55 and 87 mg. % in 4 cases.

The etiology of this condition is unknown, although a viral cause is suspected.

SIEKERT, Rochester, Minn.

SPONTANEOUS STROKES IN THE YOUNG. H. STEVENS, Ann. Int. Med. 49:1022 (Nov.) 1958.

Stevens reports a study of 32 cases of cerebrovascular accident in normotensive young adults and 2 in children, encountered in seven years of private neurologic practice. The ages ranged from 5½ to 45 years. All subjects were ambulatory and active.

Two large categories were recognized—strokes due to venous and strokes due to arterial thrombosis. Subheadings of the former included (*a*) infantile hemiplegia, (*b*) puerperal hemiplegia, and (*c*) venous thrombosis of pregnancy. The arterial thromboses were subdivided into (*a*) carotid artery lesions, (*b*) middle cerebral artery lesions, and (*c*) lesions of other arteries of the circle of Willis, single or in combination. The author feels that puerperal hemiplegia is probably the commonest form of spontaneous stroke in healthy women and that it is due to cortical venous thrombosis.

Five cases are presented in more detail, the ages being 24, 37, 25, 35, and 39 at the time of onset. The diagnostic criteria are reviewed, and the treatment with anticoagulants is appraised.

The author believes that most arterial strokes in the healthy young are due to solitary atheromatous plaques, similar to those found in older patients. Stress seems to precipitate the attack in some cases.

AIGNER, Rochester, Minn.

HYPERTENSIVE CEREBROVASCULAR DISEASE: A CLINICAL AND PATHOLOGIC REVIEW OF ONE HUNDRED CASES. A. J. HUDSON and H. H. HYLAND, Ann. Int. Med. 49:1049 (Nov.) 1958.

Hudson and Hyland review 100 cases of hypertension with autopsy, chiefly with regard to neurologic features. The hypertension was not exclusively of the "essential" variety but included cases with renal disease.

The average duration of known hypertension was 7.2 years. The average systolic blood pressure for the series was 220 mm. and the diastolic pressure 126 mm., with a standard deviation of 20.16 for the systolic and 17.36 for the diastolic.

Of the patients, 57 were men and 43 were women. The average age was 55.8 years, and the average age of death was 56 for the men and 55 for the women.

The chief initial symptoms were shortness of breath with effort (46%), stroke (16%), and headache (14%). Of those that presented with strokes, three-fourths died of a cerebrovascular accident.

Cerebrovascular accidents were considered as (*a*) those due to vascular insufficiency or occlusion, and (*b*) those due to hemorrhage. In 85% of the entire series cerebral lesions were due to hemorrhage or softening, found at autopsy. In one-fourth of these (21 cases) small softenings were found at autopsy without history of any clinical incident or focal neurologic findings; most of those with a history of stroke had, in addition to the causative lesions, other lesions which could not be correlated with the clinical history.

Of the whole series, 47% had a history of stroke which was considered to be due to vascular insufficiency or occlusion. Of the entire series, 31% showed that death was due to a large intracranial hemorrhage. Ten cases were discovered to have had an intracranial hemorrhage of a size sufficient to impair consciousness or motor or sensory function without a fatal outcome.

Defining hypertensive encephalopathy as an acute transitory disturbance of cerebral function occurring with severe hypertension and characterized by drowsiness, headache, vomiting, and various focal manifestation, including amaurosis, hemiplegia, and sometimes convulsions, the authors found only one case in which this diagnosis could be made with reasonable assurance.

The authors found that 18% of their series showed definite evidence of dementia, which ranged from failing memory and mental slowing to gross deterioration, requiring institutional care. Sixty per cent of the cases gave headache as a significant aspect of their illness. Ophthalmoscopic examination showed that 87% had fundal changes indicative of hypertension by the time of death; 65% retinal hemorrhage, and 55% papilledema. Retinal exudates were seen in 53%. Epileptic convulsions occurred in 20 cases, and 9 of these were focal in onset.

AIGNER, Rochester, Minn.

SUBDURAL HEMATOMA RELATED TO ANTICOAGULATION THERAPY. M. NATHANSON, H. CRAVIOTO, and B. COHEN, Ann. Int. Med. 49:1368 (Dec.) 1958.

The authors report two cases of subdural hematoma occurring spontaneously in patients on bishydroxycoumarin (Dicumarol) therapy for myocardial infarction. Although a history of head trauma is not available, the authors suggest the possibility that minor trauma to the head, easily unobserved, may initiate oozing of blood that continues uncontrolled in patients on anticoagulant therapy. They believe that a subdural hematoma should be considered as a complication of bishydroxycoumarin therapy whenever mental and neurologic signs develop during the course of such treatment.

AIGNER, Rochester, Minn.

CONVULSIVE SEIZURES AFTER ADMINISTRATION OF CHLORPROMAZINE. O'N. BARRETT JR., J. A. M. A. 166:1986 (April 19) 1958.

One of the complications of chlorpromazine which is potentially rather serious is the epileptogenic effect of this agent. This effect has been noted primarily in patients with latent or overt convulsive disorders.

Barrett describes two cases in which convulsions apparently were precipitated by the administration of chlorpromazine. The first patient, a 32-year-old man with a history of chronic alcoholism, was admitted because of vomiting and hematemesis after a heavy alcoholic bout. Intravenous fluids, and two doses of 25 mg. of chlorpromazine intramuscularly were given, with a five-hour interval between doses. Within 24 hours the patient developed a Jacksonian-type seizure of the right side, which progressed into a typical grand mal attack. No further chlorpromazine was administered, and no further convulsions were noted. An electroencephalogram done four days after the seizure showed "evidence of a convulsive disorder compatible with epilepsy." The patient had no further seizures during a three-month follow-up period.

The second patient was a 66-year-old woman admitted because of nausea, vomiting, and a "convulsion," apparently occurring after a dietary indiscretion. Her past history revealed only infrequent headaches and occasional spells of "lightheadedness," but no evidence of a convulsive disorder. A local physician had administered 25 mg. of chlorpromazine intramuscularly. Within 10 minutes she had a grand mal seizure. An electroencephalogram made two days later revealed "an abnormal awake and sleep pattern consistent with a convulsive disorder." The patient remained asymptomatic during four months after discharge.

Barrett stresses the more careful screening of patients prior to the administration of this drug.

ALPERS, Philadelphia.

CEREBRAL VASOSPASM—CLINICAL AND EXPERIMENTAL EVIDENCE. J. L. POOL, S. JACOBSON, and T. A. FLETCHER, J. A. M. A. 167:1599 (July 26) 1958.

The authors describe clinical and experimental observations which indicate that the larger cerebral arteries in man and three different species of animals are capable of vasoconstriction when subjected to similar types of artificially imposed mechanical stimuli. Vasodilatation can be induced by topical application of 2% procaine hydrochloride or 3% papaverine hydrochloride after dissection or test stimuli have caused vasospasm.

Since procaine acts primarily on nerves and nerve endings, and papaverine on smooth muscle, this work suggests that the observed changes in contractibility of the larger cerebral arteries may be mediated both by their local intrinsic nerve supply and by their smooth muscle fibers, both in animals and in man. Of these two factors, the smooth-muscle response is more powerful than neurogenic regulation of cerebral arteries.

These observations indicate that the basal cerebral arteries are capable of vasospasm and react to trauma as do other arteries of the body. This response to trauma appears to be the same whether the stimulus is mechanical, during an experiment, or is a result of a disease process, such as rupture of aneurysm, perivascular hemorrhage, or, perhaps, other pathological conditions.

ALPERS, Philadelphia.

HEMICHOREA (HEMIBALLISMUS) WITHOUT LESIONS IN THE CORPUS LUYSII. J. P. MARTIN, Brain 80:1 (March) 1957.

Martin reports three cases of hemichorea in which the subthalamic body of Luys was found to be intact at postmortem examination. In the first case thrombosis of the posterior cerebral artery was found, with microscopic examination of the basal ganglia revealing an area of degeneration medial and posterior to the corpus Luysii, but the corpus Luysii itself was intact. In the second case, a vascular lesion was found which involved the anterior margin of the corpus Luysii and produced hemichorea with an intact subthalamic body. The third case of hemichorea was associated with thrombosis of the internal carotid artery, which produced ischemia of the corpus Luysii but no degeneration.

Martin concludes that these findings coincide with the physiological findings of Whittier and Mettler, who noted that when the connecting fibers between the corpus Luysii and the globus pallidus are interrupted the controlling influence of the former is removed and hemichorea results. The hemiballismus which occurs in such patients is not as violent as when the corpus Luysii itself is involved.

MANDEL, Philadelphia.

BEHCET'S SYNDROME WITH NEUROLOGICAL COMPLICATIONS. N. WADIA and E. WILLIAMS, Brain 80:59 (March) 1957.

Behcet's syndrome, consisting of oral and genital ulceration with hypopyon iritis, occurs rarely with involvement of the central nervous system. The authors report three cases of Behcet's syndrome with diffuse central nervous system involvement and compare their findings with the 10 previously reported cases.

Of the 13 patients, 8 were male and 5 female, the ages ranging from 16 to 47 years. The neurological symptoms occurred acutely, and recurrent attacks were usual, the number in each case varying from one to seven. Headache was a symptom in the majority of cases, and a clinical diagnosis of meningitis was made in four cases, the cells counts of the spinal fluid being elevated and predominantly lymphocytic in each instance.

Brain-stem involvement was present frequently, bilateral ocular pareses, nystagmus, and dysphagia being common symptoms. Eight patients, including two in this series, had spastic weakness involving one or more limbs. Dementia was also present as a common neurological complication.

MANDEL, Philadelphia.

RATHKE-POUCH TUMORS. D. W. C. NORTHFIELD, Brain 80:293 (Sept.) 1957.

Northfield reviews his clinical experience in 49 cases of Rathke-pouch tumors over a 23-year period. In this series, 26 patients were male and 23 female, with ages varying between 3 and 56 years. There were 28 deaths and 11 survivors, and the remainder, who were unheard from, were assumed to be dead.

Although the clinical symptoms varied considerably, the majority of patients had visual impairment and headache as initial symptoms. Other symptoms of particular interest were

hallucinations, epilepsy, and mental impairment. Visual hallucinations were found in five cases, with olfactory and gustatorial hallucinations noted in two others. In the latter instance, the tumor was subtuberal in location. Epilepsy developed spontaneously in seven cases as a result of the tumor, all of the seizures being of a generalized nature, but none were suggestive of diencephalic rage. Mental symptoms, varying from mental dullness to severe dementia, were also found in 14 cases. Endocrine symptoms, consisting of sexual immaturity with long extremities and fingers, were noted in the majority of cases. Diabetes insipidus was found in 13 cases.

An analysis of 46 operations in 32 cases showed 16 deaths. Northfield reports the use of radioactive gold in two cases of Rathke-pouch tumors with direct injections into the tumor. The results are too early for evaluation, but improvement was noted in both cases.

MANDEL, Philadelphia.

SYMMETRICAL CALCIFICATION OF THE BASAL GANGLIA WITH FAMILIAL ATAXIA AND PIGMENTARY MACULAR DEGENERATION. R. R. J. STROBOS, E. DE LA TORRE, and J. F. MARTIN, Brain 80:313 (Sept.) 1957.

The authors report symmetrical calcification in the basal ganglia in roentgenograms of the skull of two brothers who were afflicted with familial ataxia. This condition was also associated with impairment of central vision, due to pigmentary macular degeneration.

The literature relevant to symmetrical calcification in the basal ganglia is reviewed. This finding has been described in cases of idiopathic hypoparathyroidism, as well as many other conditions, including toxoplasmosis and tuberous sclerosis.

MANDEL, Philadelphia.

PRIMARY ARACHNOID CYSTS. L. C. OLIVER, Brit. M. J. 1:1147 (May 17) 1958.

Case reports of intracranial primary arachnoid cysts in the literature lend support to the view that these cysts are not of inflammatory origin, but histologic reports on the membranes are rarely given. For this reason, Oliver reports two surgical cases in which he describes the cysts and the histologic picture in detail. One cyst was in the Sylvian fissure and the other in the posterior fossa. Oliver suggests that arachnoid cysts of unknown origin be called primary arachnoid cysts, and those which are due to inflammation or injury or are associated with tumors be called secondary arachnoid cysts. Oliver suggests that primary cysts may result from an error of development of the leptomeninges and the underlying nerve tissue.

ECHOLS, New Orleans.

THE GREAT TOE-JERK. G. A. RANSOME, Brit. M. J. 2:548 (Aug.) 1958.

Ransome describes a phenomenon which, although not new, he has never seen used elsewhere or described in standard textbooks. It is the great-toe dorsal spring reflex (extensor hallucis longus), which he believes will eventually become part of the routine physical examination. Its root value is the fourth and fifth lumbar, and it is most useful as an objective sign in disk lesions between the fourth and fifth lumbar vertebrae, as it is abolished early in this condition, even before objective weakness can be demonstrated.

To obtain this reflex with ease requires a great deal of practice. It is elicited in the following manner: With the patient lying flat in the dorsal position and the foot extended and slightly inverted, the index finger of the examiner's right hand is placed on the terminal dorsal surface of the terminal phalanx of the great toe. Downward pressure is exerted until a feeling of elastic stretch is obtained. Using a wrist follow-through movement, the examiner then strikes his index finger with the hammer; the great toe can be seen and felt to extend if the maneuver is properly performed.

ECHOLS, New Orleans.

ACUTE PSYCHOSES DUE TO ENCEPHALITIS FOLLOWING ASIAN INFLUENZA. E. BENTAL, Lancet 2:18 (July 5) 1958.

Bental reports three cases of acute psychosis coming on after Asian influenza in three children under the age of 16. The psychotic manifestations occurred from 2 to 10 days after the onset of the influenza, and the manifestations were almost identical in all the cases, including signs of acute anxiety, confusion, extreme restlessness, and ideas of persecution. The acute psychosis was apparently the only clinical manifestation of encephalitis. The psychotic symptoms receded within six to eight days, leaving the patients with complete amnesia

for the acute phase of the illness. Another feature common to all the cases was the diffusely abnormal electroencephalograms, which remained abnormal long after the clinical recovery of the patients.

YASKIN, Camden, N. J.

NEUROLOGICAL SYNDROMES ASSOCIATED WITH CARCINOMA: THE CARCINOMATOUS NEUROMYOPATHIES. R. BRAIN and R. A. HENSON, Lancet 2:971 (Nov. 8) 1958.

Brain and Henson review the problem of central nervous system involvement in patients suffering from carcinoma, independent of the presence of metastases. They survey 42 cases in which neurological disorders were exhibited in association with carcinoma in the absence of relevant metastases. They use the term carcinomatous neuromyopathy to describe the entire group. They classify this group of disorders as follows: cortical cerebellar degeneration (with widespread loss of Purkinje cells), sensory neuropathy, peripheral neuropathy (sensorimotor), neuromuscular disorders, and mixed forms.

There is no constant relationship between the course of the neurological disorder and that of carcinoma. Although the neuromyopathy may develop pari passu with the tumor, neurological symptoms may antedate the clinical manifestations or diagnosis of the growth by a period of at least three years. Exceptionally, the neuromyopathy may arise after the successful removal of the cancer. Patients with neuromuscular disorders or mixed forms of peripheral neuropathy have shown striking remissions, and even recovery from their neurological symptoms, at times when they have been seriously ill and near death from the effects of the growth. Again, there is no relation between the size of the cancer and the severity of the neuropathy. Occasionally, the neurological picture develops in the terminal stages of the carcinoma. In this series there were eight cases of cortical cerebellar degeneration as a complication. Clinically, the picture was one of subacute, or even acute, cerebellar disorder. Vertigo, ataxia, severe cerebellar deficit in the limbs, dysarthria, diplopia, and nystagmus were the characteristic features. Mental changes have been prominent. Postmortem examination in three cases revealed a striking loss of Purkinje cells in the cerebellar cortex.

Seven patients in their series are classified as belonging to the mixed form ot complications. The clinical findings in these patients are as varied as the pathological findings which have been found post mortem. Findings were degeneration of the motor cells of the spinal cord and brain-stem nuclei, degeneration of the pyramidal tracts and posterior columns of the spinal cord, and cellular infiltration of the meninges and perivascular cupping of the vessels of the spinal cord and of the medulla below the floor of the fourth ventricle. Cerebellar signs are present in all, though less prominently than in the first group. Muscular wasting and weakness affect the limbs. Bulbar palsy, ptosis, and weakness of external ocular movements also occur. Involuntary movements may be prominent. Pain and dysesthesiae in the limbs may be severe; impairment of postural and vibratory sense and, less commonly, cutaneous sensory loss of peripheral distribution are found. Again, mental change may be prominent.

Five patients are classified under the peripheral neuropathy group with sensorimotor disturbances. Another subgroup is the sensory type in which the pathological picture consists in degeneration and loss of neurons in the posterior root ganglia, with associated degeneration of the peripheral nerves and posterior columns. Some of the patients in the mixed group had a motor neuropathy, inasmuch as their muscular weakness was due to a loss of anterior horn cells. Another group was classified as neuromuscular in type. These patients had generalized muscle atrophy with some degree of enfeeblement.

Abnormalities were found in the cerebrospinal fluid of five of eight patients with cortical cerebellar degeneration and in four out of seven with the mixed types. The changes included lymphocytic pleocytosis, with up to 48 cells per cubic millimeter, increased protein (as high as 120 mg. per 100 ml.), and Lange curve of paretic type. The Wassermann reactions of the blood and cerebrospinal fluid were always negative. A raised protein content, rarely with cellular increase, was common in sensory and sensorimotor peripheral neuropathy. The cerebrospinal fluid was normal in all patients with carcinomatous myopathy. The authors emphasize that the etiology of these neurological syndromes remains obscure.

YASKIN, Camden, N. J.

THE NATURAL HISTORY OF HYDROCEPHALUS. K. M. LAURENCE, Lancet 2:1152 (Nov. 29) 1958.

Laurence reviewed 182 unselected and nonsurgical cases of hydrocephalus seen by one surgeon during the past 20 years. Of these patients, 89 had died; in 81 the condition had become

arrested spontaneously, and in 9 it was progressive; 3 had not been traced, but were probably alive. Of the traced survivors with spontaneous arrest, 75% are educable, and the intelligent quotient of 57% fell within the normal range (I. Q. 85 and above). This investigation suggests a more hopeful prognosis, for an appreciable number of these cases have not only survived but are now growing into useful citizens capable of earning their living. Further, in view of the spontaneous-arrest rate of 46%, the reported results of surgery in hydrocephalus may have to be reassessed.

This author states that should a hydrocephalic child survive to have a spontaneous arrest he has a 75% chance of being educable, and a 57% chance of being taught, apart from his physical handicap, in a school for normal children. In fact, of the 81 children with arrested hydrocephalus which were traced, 25 were children of normal intelligence, with negligible or no physical handicap.

YASKIN, Camden, N. J.

SYMMETRICAL INTERNAL HYDROCEPHALUS IN CAUSATION OF CONSEQUENCES OF CLOSED HEAD INJURIES. J. KRISCHEK, Psychiat. et neurol. 136:145 (Sept.) 1958.

Krischek describes the critical value of cerebral pneumography in the assessment of brain damage following head injuries. Intelligent management of head injuries demands understanding of the following three problems: The force of injury, the sequence and rate of development of symptoms, and the nature of any constitutional anomalies and deficiencies antedating the injury. Krischek points out that the incidence of asymmetrical variations in the ventricular silhouette is rather high in the last-named conditions. The demonstration of this finding within weeks after injury in the presence of normal electrophoretic β- and τ-fractions of the spinal fluid is particularly suggestive, especially in the presence of a clinical picture replete with subjective complaints and with few objective findings. In the event of elevated β- and τ-fractions, the early pneumographic abnormality described is more likely attributable to a progressive premorbid cerebral sclerosis or encephalitis. When air studies are performed months or years following injury, the visualization of circumscribed or diffuse ventricular enlargement is suggestive of significant focal or generalized cerebral atrophy, especially in the presence of normal values for fluid β- and τ-fractions. These findings, in turn, are closely correlated with the clinical course characterized by relatively major disturbance in consciousness and significant objective findings. It is the author's opinion that pneumographic variations thus provide necessary supplemental information assisting the clinician in understanding why some patients seem not only more "accident prone" but also less capable of recovery from relatively trivial assault. The article is unaccompanied by illustrative roentgenograms, case reports, or corroborative statistics.

PARSONS, Montrose, N. Y.

News and Comment

ANNOUNCEMENTS

The Academy of Psychosomatic Medicine.—The Sixth Annual Meeting of The Academy of Psychosomatic Medicine will be held Oct. 15-17, 1959, at the Sheraton-Cleveland Hotel, in Cleveland. The meeting will be oriented and directed to fit the needs of nonpsychiatric physicians. Practical everyday office management of psychosomatic problems and emotional disturbances will be dealt with in formal papers, symposia, panel discussions, and small study groups.

The meeting will be open to all scientific disciplines, as well as psychologists, social workers, and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 E. Washington St., Chicago 2.

Second International Congress of Neurological Surgery.—The Second International Congress of Neurological Surgery, sponsored by the World Federation of Neurosurgical Societies, will take place at the Hotel Statler, Washington, D. C., Oct. 14-20, 1961, under the presidency of Dr. Paul C. Bucy. All neurosurgeons of the world are invited to attend. A stimulating scientific program and pleasant social activities are being developed by the officers and the organizing committees. Important fields of neurosurgery will be discussed by distinguished authorities, and a closed-circuit television program of surgical procedures will be presented daily. A detailed program will be published in this journal early in 1960. All correspondence concerning the Congress should be addressed to the Secretary-General, Dr. Bronson S. Ray, 525 E. 68th St., New York 21.

SOCIETY NEWS

Illinois Psychiatric Society.—On April 15, 1959, the following members of the Illinois Psychiatric Society were elected to office for the year 1959-1960:

President ..... Dr. Frances Hannett
5490 S. Shore Dr.
Chicago 15

President-elect ..... Dr. Joel S. Handler
670 N. Michigan Ave.
Chicago 11

Secretary-treasurer ..... Dr. Paul Nielson
912 S. Wood St.
Chicago 12

Councilors ..... Dr. Nathaniel S. Apter
111 N. Wabash Ave.
Chicago 2
Dr. C. Knight Aldrich
950 E. 59th St.
Chicago 37

Serving their third year of a three-year term are Dr. John R. Adams, 720 N. Michigan Ave., Chicago 11 (delegate to American Psychiatric Association Assembly) and Dr. Isadore Spinka, 6500 Irving Park Blvd., Chicago 34 (alternate delegate to American Psychiatric Association Assembly).

The Western Neurosurgical Society.—The Western Neurosurgical Society will meet this year at the La Valencia Hotel, La Jolla, Calif., Sept. 27 through 30. Dr. Ernest W. Mack, Secretary, 505 S. Arlington Ave., Reno, Nevada.

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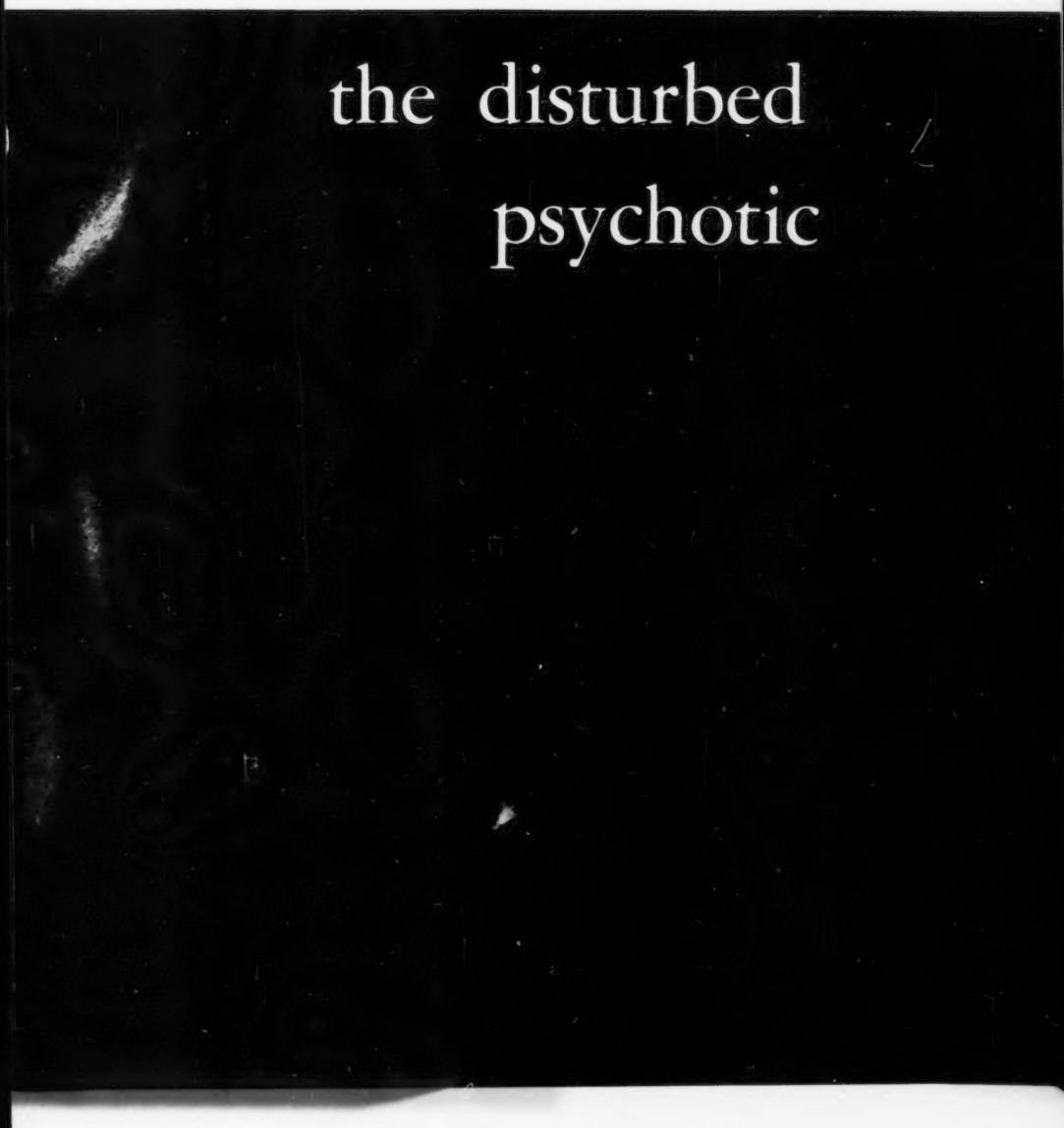

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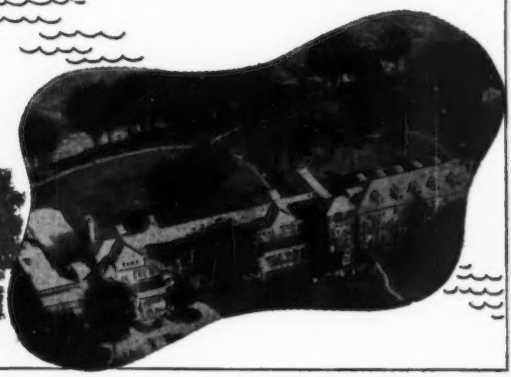

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References: 1. Vorbusch, H. J.: J. Clin. & Exper. Psychopath., (Jan.-Mar.) 1959
2. Feldman, P. E.: Am. J. Psychiat. *115*:736 (Feb.) 1959.

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